Endometriosis in Adolescents

A Comprehensive Guide to Diagnosis and Management

Ceana H. Nezhat *Editor*

Jennifer Dietrich
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Foreword

For more than a century, endometriosis was believed to occur after 20–23 years of age. In a series of 400 cases published by J.V. Meigs, only 1 was less than 29 years old. In a larger series of 884 cases of the Mayo Clinic, the youngest patient was 21, and Sampson himself remembered no patient younger.

Fallon J. in his endometriosis series of 225 cases published in *JAMA* in 1946 reported 9 patients (4%) to be less than 20 years of age. He states further *"4% is a small figure, but there are grounds for suspecting that it is less than the true one. And it is a significant, even a large percentage when weighed against the common belief that youth does not have endometriosis."* None the less, despite this observation and warning, the practice did not change for many decades, and diagnosis and treatment were delayed in adolescents suffering from endometriosis.

We must welcome this new book *Endometriosis in Adolescents: A Comprehensive Guide to Diagnosis and Management* initiated and edited by Professor Ceana Nezhat, who also contributed several chapters to it.

This book, with its 45 chapters, is certainly comprehensive and richly illustrated; it is also unique in style and content. The authorship is international and well-recognized in their own fields of expertise. The book is organized into 13 parts. Following an interesting introduction by Dr. Ceana Nezhat, two comprehensive previously published articles composed by the Nezhat brothers are included in Part 1, History of Endometriosis in Adolescents. Another such article "Optimal Management of Endometriosis and Pain" is included in Part 3. An additional novelty of the book is the inclusion of three "patient histories." The part on etiology has chapters on molecular mechanisms, pathophysiology, and endometriosis in the human fetus.

The text contains unexpected sections that complement the disease itself, such as "Associated pathology in adolescents—Thyroid disease, PCOS, Adnexal tumors etc.-; plus, "Anesthetic considerations and Patient positioning" for pediatric and adolescent gynecologic surgery. In Part 11, Interventions, one is surprised to find interesting chapters on topics other than surgical intervention, such as impact of nutrition on adolescent endometriosis, effect of curcumin on endometrial stomal cells, and holistic approach for management of the disease. In addition, a chapter on

the approach to diagnosis of adolescent endometriosis for primary care pediatricians is included in the final part of the book.

Undoubtedly, this timely and excellent book will be a must for those involved and interested in pediatric and adolescent endometriosis.

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Foreword

Once again, the name Nezhat has been associated with an imaginative, revolutionary and important topic to investigate and to inform. In the past, endometriosis was thought to be confined to older women (over 35) who were nulliparous. Described by the Greek term Sylph.

Ceana Nezhat and his collaborators have re-defined all aspects of endometriosis focused on the adolescent, which now is accepted to be a part of the population who suffer from endometriosis. Still overlooked in this population, because education is necessary to alert the practitioner, that these young women do get endometriosis during adolescence. In fact, when examining older women with endometriosis, many attest to the fact that their symptoms started in adolescences and endometriosis was not considered a serious diagnostic option. Therefore, there is a tremendous delay in the diagnosis of this progressive disease.

Pain and abnormal bleeding being the hallmarks. Early diagnosis is important to allow for rapid and effective treatment and to prevent scarring from occurring. Hormonal and non-hormonal approaches should be utilized.

Endometriosis in the adolescent has severe ramifications. Missed school days and activities are obvious, but other social connotations are also prevalent including psychological and social impacts. Chronic pain affects adults as far as carrying out usual functions, well this is no different for adolescents with endometriosis.

On perusal of the contents of this text, many important questions are raised and addressed in an erudite fashion. This is an extremely studied field now with emphasis on endometriosis as an inflammatory disease. In regards to diagnosis, the quest for markers in the bloodstream is an area of active searching so that the diagnosis can be made more precisely to remove the need for surgical intervention to diagnose endometriosis. Although, the Lupron challenge test in today's environment is highly acceptable.

Much is to be learned from patients with Mullerian anomalies as far as the pathogenesis of endometriosis is concerned and this is covered in the text.

Is a new classification paradigm necessary?

Fertility remains an important area for the patient with endometriosis. If it could be treated early in the adolescent women, it would be extremely beneficial to the adult women trying to conceive; because the questions arise: Are oocytes from a patient with endometriosis normal? Are there implantation problems since the endometrium of a patient with endometriosis is different, e.g. aromatase activity.

Still the most controversial area is the role of surgery in either laparoscopic or open procedure to treat endometriosis.

Drugs and drug development in regards to this disease are critical.

All in all, endometriosis is a fascinating disease with basic science questions, translational questions, therapeutic and diagnostic questions. There is a major effort to study endometriosis in all aspects and this well written and comprehensive book will be extremely helpful to those investigators and practitioners who deal with endometriosis in the adolescent.

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Chapter 1
Preface

Ceana H. Nezhat

"How much or how bad is my endometriosis?" Let's put it like this, a little bit of cyanide or a lot of cyanide is not good.

—Ceana H. Nezhat MD

A silent and debilitating disease, endometriosis has long been thought to affect mostly adult women. However, it does not discriminate against age. Rates of video laparoscopically confirmed endometriosis among adolescent females with pelvic pain ranging from 19% to 73% [1–3] as well as roughly 10–15% of all reproductive-aged women and approximately 35–50% of women with pelvic pain and infertility. Lack of awareness by both physicians and patients can lead to delayed diagnosis and potentially erroneous recommendations. Ill advice, such as "diet has nothing to do with endometriosis" or referring a patient to a psychiatrist because her severe pain is not responding to a particular treatment, can have devastating long-term consequences particularly in adolescents. Women with endometriosis have been shown to have higher likelihoods of prolonged use of opioids and concomitant use with benzodiazepines compared to women without endometriosis [4].

Extragenital endometriosis can manifest in almost any part of the body outside the reproductive system, most commonly in the gastrointestinal and urinary tracts, with cases reported in the lungs, diaphragm, etc. Diagnosis can be difficult as lesions are usually undetectable by exam, laboratory studies, or imaging. Surgical evaluation with high-definition or 3D videolaparoscopy with or without robotic-arm assistance for simultaneous diagnosis and treatment is the gold standard at this time.

Endometriosis in Adolescents: A Comprehensive Guide to Diagnosis and Management highlights a commonly overlooked disease in a vulnerable population, our children. Persistent chronic pelvic pain despite medical treatment (i.e., dysmenorrhea and acyclic chronic pain), abnormal/irregular uterine bleeding, and

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dyspareunia, as well as genitourinary, gastrointestinal, and constitutional complaints, are the most commonly reported endometriosis-related symptoms in adolescents [5]. While most women report first onset of endometriosis-related symptoms during adolescence, diagnosis on average takes 6–10 years. Those who seek treatment in adolescence experience a more difficult path to diagnosis than women who first report symptoms as adults. This delay is attributed to a variety of causes including lack of awareness or knowledge and physician doubt in patient-reported pain. Adolescents suffering from a delay or lack of diagnosis may experience erroneous treatments and referrals, unnecessary imaging and radiation exposure, increased school absenteeism, emergency department visits, and early exposure to narcotic pain medications. As a result, young girls suffer from stigmas, and many are not taken seriously by their physicians. Far too often I hear patients say they have been told "nothing is wrong" by previous physicians or "it's all in your head."

A patient of mine began having "stomach issues" in fourth grade. Her doctors failed to determine the source of her lower abdominal pain, and throughout her teenage years, she received a range of misdiagnoses from irritable bowel syndrome to lactose intolerance. Finally, at age 18, her primary care physician suspected she may have endometriosis, yet still she remained undiagnosed. Three years later, she was diagnosed with polycystic ovary syndrome (PCOS) and prescribed birth control pills as a treatment. However the pills were no cure, and—as she later learned—PCOS was an incomprehensive diagnosis.

In 2000, at age 21, she underwent her first surgery to lance PCOS-related cysts. During the procedure, her endometriosis was discovered. Eleven years after her abdominal pain began, and 3 years after it was first suspected, she was finally accurately diagnosed. Her doctor told her the surgery would resolve both her PCOS- and endometriosis-related issues, but the pain—which some doctors told her was only in her head—continued. She was continuously assured it was impossible that the endometriosis had come back. She was put on hormones and anxiety medication and instructed to do pelvic floor exercises.

Five more surgeries, including a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and 7 years later, she walked into my office. I discovered an ovarian remnant requiring complete removal and radical treatment of extensive endometriosis which was left behind due to the location and assumption that hysterectomy would take care of it. This was the solution for which she had searched endlessly. In her own words, "Since my surgery with Dr. Nezhat, I am a different person. I am happily married and more confident in myself and full of joy. Ten years ago, my life without pain began."

I want to inspire physicians worldwide to learn more about the disease and better understand its massive impact. Increasingly the rate of early detection of endometriosis is the first hurdle. When discovered early, irreversible damage can often be prevented, and a patient's quality of life can be preserved.

Often a progressive disease, endometriosis in adulthood is the third leading cause of gynecologic hospitalizations and is associated with chronic pelvic pain, diminished quality of life, sub-fertility, psychological morbidity, and reduced work attendance. If left undiagnosed and thus untreated, it can damage affected organs, spread

to surrounding tissues, and negatively impact future fertility. Here are several examples of endometriosis progression.

Partial Ureteral Obstruction

A 42-year-old nulligravida with chronic pelvic pain since menarche. Preoperative intravenous pyelogram showed a partial obstruction and constriction of the mid-pelvic and distal portion of the left ureter with proximal hydroureter, compatible with extrinsic ureteral compression (Fig. 1.1).

She underwent video laparoscopy. The endometriosis was resected using hydrodissection and shaving with CO_2 laser. Histopathologic evaluation of the resected specimens confirmed endometriosis (Figs. 1.2 and 1.3).

Fourteen years later, she remains asymptomatic. A follow-up intravenous pyelogram was performed and showed a normal urinary tract with bilateral ureteral patency and no recurrent strictures (Fig. 1.4).

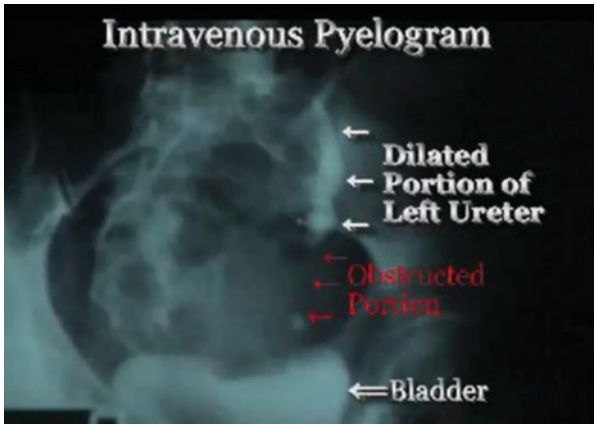

Fig. 1.1 Preoperative IVP at first surgery for partial obstruction and constriction of the mid-pelvic and distal portion of the left ureter

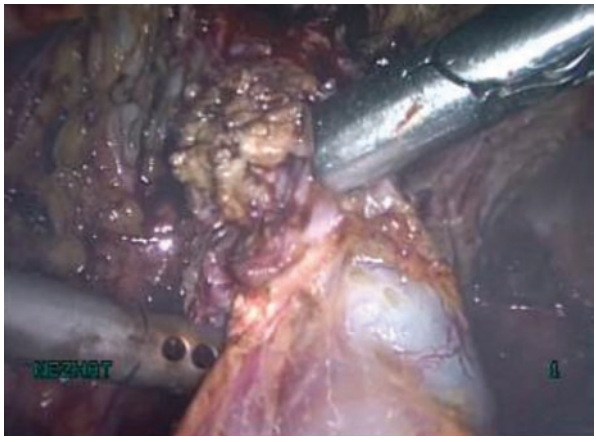

Fig. 1.2 Distal left ureter encased in endometriosis and fibrotic tissue with proximal hydroureter

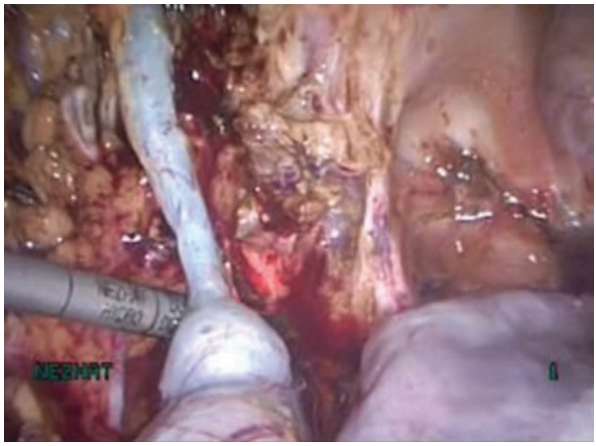

Fig. 1.3 After meticulous dissection and mobilization of the ureter, the point of stricture is clearly seen with persistent proximal dilatation

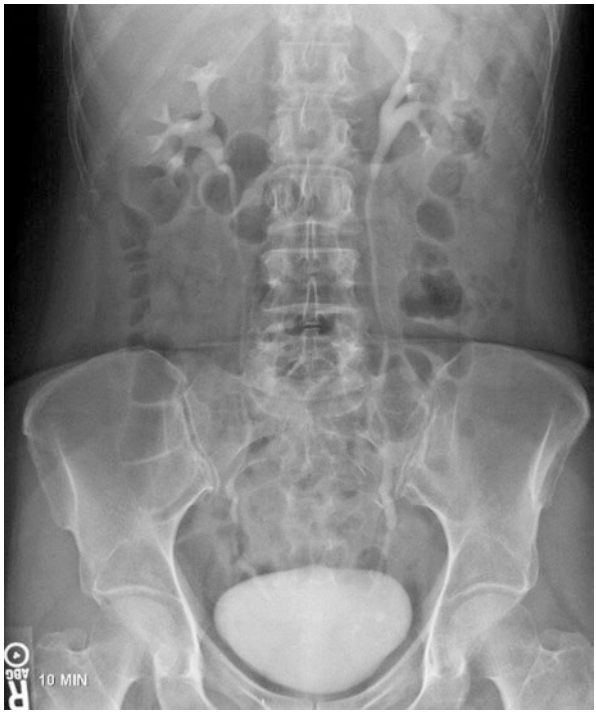

Fig. 1.4 IVP after 14 years on second look

Hematoureter Resulting in Lost Kidney

Link to video [6] – https://doi.org/10.1016/j.fertnstert.2014.02.049

A 17-year-old female with uterine didelphys, history of left nephrectomy, and partial left ureter resection presents with pelvic pain. MRI (Fig. 1.5) revealed a left retroperitoneal mass with extension to the paravesical region, with reaccumulation

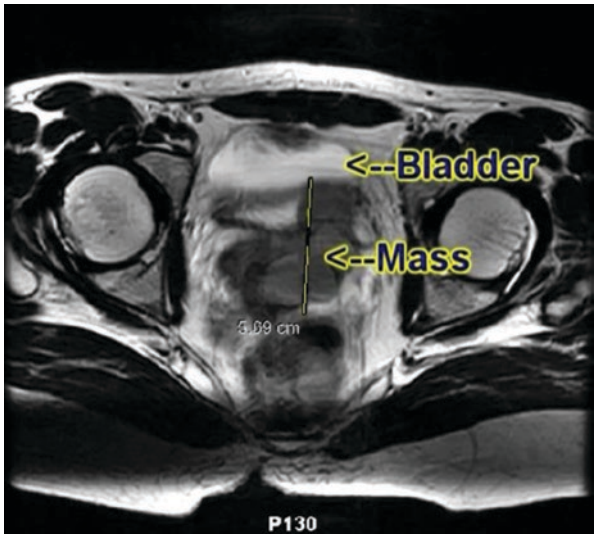

Fig. 1.5 MRI revealing a 6 × 3 × 4 cm complex mass in the left pelvic sidewall extending toward the bladder

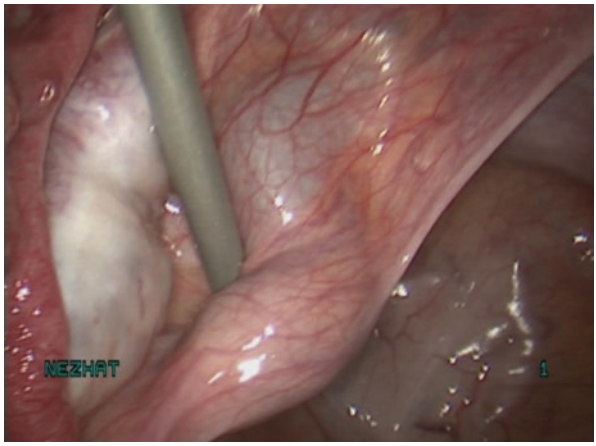

Fig. 1.6 Left hematoureter

of the hematocolpos behind the partially resected left transverse vaginal septum, and a dilated left uterine horn with hematometra.

Intraoperative findings showed a bicornuate uterus with dilated left uterine horn, normal right uterine horn, and normal right and left fallopian tubes and ovaries. The left transverse vaginal septum was resected vaginally, and the hematocolpos and hematometra were drained.

The left uterine horn and cervix were laparoscopically resected. The left-sided serpiginous (Fig. 1.6) retroperitoneal mass was dissected from the pelvic sidewall, ligated, and transected with spillage of thick, brown fluid (Fig. 1.7). The pathology of the mass wall was smooth muscle and transitional epithelium consistent with ureter in addition to hemorrhage and glandular structures consistent with endometriosis. Endometriosis was also present in the serosa of the left uterine horn. The

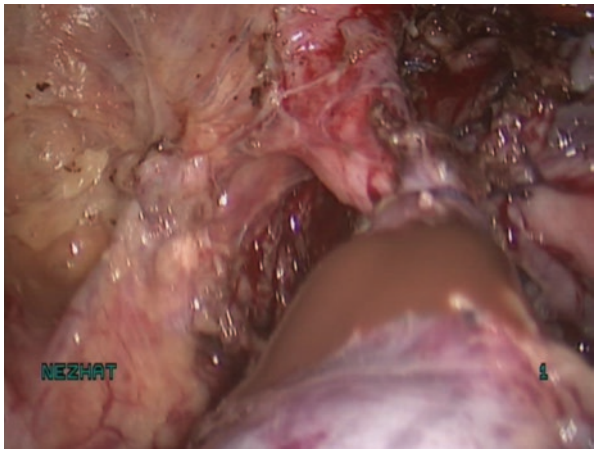

Fig. 1.7 Chocolate material exuding off the left ureter

conclusion was the left retroperitoneal mass to be remnant of the left ureter which acquired endometriosis, resulting in hematoureter.

Described within the findings of this case are two major pathological types of ureteral endometriosis: intrinsic and extrinsic. Women with Müllerian anomalies, vaginal obstruction, and imperforate hymen are at higher risk of endometriosis [7–10]. Prior urogenital surgery can further complicate and distort the anatomy. Thus, a preoperative understanding of the patient's urogenital anomalies and knowledge and suspicion for endometriosis is important in order to consider the differential diagnoses and anticipate surgical needs.

Bowel Endometriosis

In another case, a 27-year-old nulligravida presented to the emergency department with 5-day history of constipation, associated with diffuse abdominal pain, nausea, and vomiting. CT scan showed wall thickening over the rectosigmoid colon with a dilated proximal colon. An enema and manual disimpaction were attempted but unsuccessful. The general surgery, gastroenterology, and gynecology services were all consulted. A flexible sigmoidoscopy was performed, and a colonic spiral metal stent was placed. The patient was then discharged [11].

The patient self-reported always experiencing pain around menses since menarche at age 13. By the time she found the appropriate multidisciplinary surgical team, she required a segmental bowel resection. A larger portion of the bowel had to be removed beyond the actual lesion secondary to the stent which was embedded in the wall of the colon (Fig. 1.8) [11].

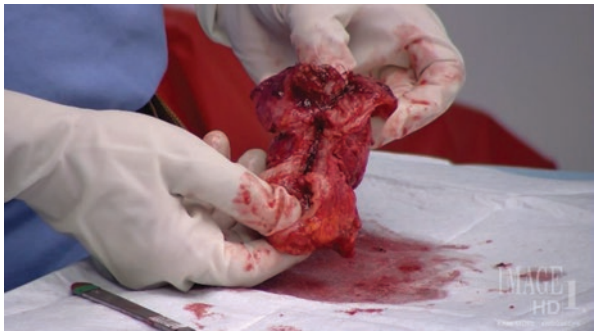

Fig. 1.8 Rectosigmoid resection specimen with rectal stent seen embedded in the colon wall

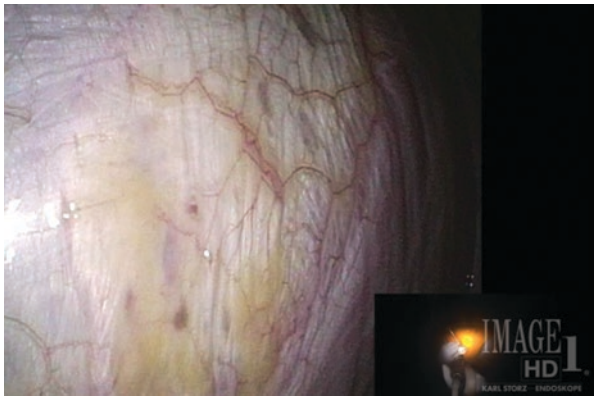

Fig. 1.9 Thoracoscopic view of right diaphragmatic multifocal endometriosis

Thoracic Endometriosis Syndrome

A 38-year-old presented with worsening symptoms and upper abdominal pain unresponsive to suppressive therapy with a history of prior laparoscopic treatment of pelvic endometriosis. She was found to have right infiltrative multilocular diaphragmatic endometriosis with liver and diaphragm as well as pelvic adhesions. Due to the involvement of the thoracic and abdominal cavities, the patient underwent a multidisciplinary approach involving thoracic and gynecologic surgeons. Video-assisted thoracoscopic surgery (VATS) with partial transthoracic diaphragm resection and mini video-assisted laparoscopic surgery (VALS) for treatment of multifocal diaphragmatic endometriosis, lysis of adhesions, as well as excision and vaporization of several fibrotic endometriosis lesions were performed (Figs. 1.9 and 1.10).

Pathology confirmed endometriosis involvement of the resected portion of the right hemidiaphragm.

These examples highlight the importance of early diagnosis and prompt intervention of endometriosis by physicians who are equipped to deal with the various manifestations.

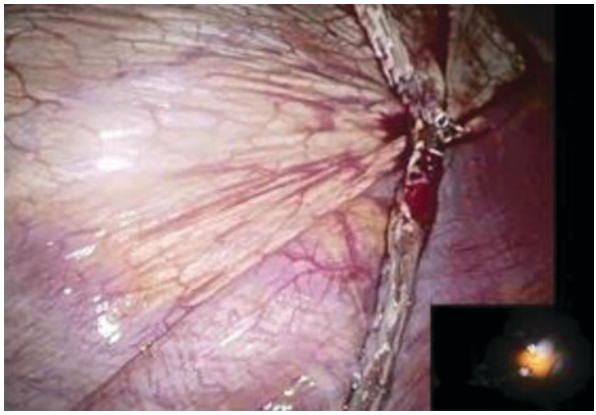

Fig. 1.10 Thoracoscopy post excision of diaphragmatic endometriosis

I believe increasing understanding of endometriosis in adolescents will provide patients and their families with faster, accurate diagnoses, which in turn leads to speedier treatment, better outcomes, and cost savings. The next generation of medical professionals has a responsibility to their patients to have a higher index of suspicion for this treatable but not curable disease.

An ideal resource for clinicians of all specialties treating adolescents, this text is a compilation of decades of expert experience presenting a clear and logical pathway through the history of endometriosis, recognition, diagnosis, appropriate interventions, as well as medical and surgical management. Principles of adolescent gynecology are presented to the healthcare providers of all disciplines who may encounter this population in their practices. The clinical matter has been humanized by stories from patients, their families, activists, and physicians. I trust the readers, both within the medical field and outside, will find this comprehensive guide useful, educational, and well-rounded.

I am thankful to all patients who entrusted me with their care and encouraged me to take on this project, especially those who shared or allowed me to tell their stories. I appreciate the editorial assistance and review provided by my associate editors, Dr. Jennifer Dietrich, Dr. Todd Ponsky, and Dr. Joseph Sanfilippo, as well as to the invited guest editors, Dr. Gwen Davis and Dr. Ralph Sams, whose combined expertise in the fields of pediatric surgery, pediatric and adolescent gynecology, minimally invasive surgery, anesthesia, pathology, and infertility brought expert-level evaluation. Special thanks to Ms. Sarah McClellan, MPH, who contributed greatly to the review process and preparation of this book. We are very proud of the depth of information we have compiled from our vanguard of contributors for you, our readers.

This book is dedicated to all patients with endometriosis and to those who care for them.

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Part I
History of Endometriosis in Adolescents

Chapter 2
Endometriosis: Ancient Disease, Ancient Treatments

Camran Nezhat, Farr Nezhat, and Ceana H. Nezhat

Ever since Vincent Knapp published his 1999 article "How old is Endometriosis?" [1], there seems to have been renewed interest in identifying just when endometriosis was discovered as a distinct disease entity.

While the history of endometriosis subsequent to its 1860 microscopic unveiling by Karl von Rokitansky has been well-studied, its story leading up to that moment has remained largely unknown. The time seemed ripe to cast light on this chasm of history and give voice to the inaudible narratives of illness that have been lost in the margins of centuries. Inexact as the study of history may be, nevertheless clinical observations from the past may offer unique perspectives that would otherwise have been entirely overlooked.

Moreover, in surveying the historical development of scientific medicine, it is evident that nearly all of our current understandings of complex disease states have resulted from the synthesis of centuries of observations. Even medical theories that ultimately proved to be exquisite fallacies have actually served as essential

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The authors have nothing to disclose.
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counterpoints throughout the ages, refining knowledge by producing the searing clarity that only unanticipated failures can yield; the sort of shock medicine sometimes needs to achieve transformative change. Viewed in this light, to exclude the formative years leading up to the microscopic discovery of endometriosis is to deprive our discipline of an invaluable reservoir of knowledge that may reveal essential, new insights about a disorder that continues to reign as one of gynecology's most perplexing diseases.

Solving the Mystery of Hysteria

Was Freud Wrong Yet Again?

With these ideas in mind, we applied a broader set of criteria in searching historical records for the earliest possible signs of endometriosis, taking care to include historical descriptions of clinical and macroscopic findings that corresponded to contemporary understandings. Historical perspectives on pelvic pain in women have also informed our analyses.

By applying this broader set of criteria, we were able to uncover substantial, if not irrefutable, evidence that hysteria, the now discredited mystery disorder presumed for centuries to be psychological in origin, was most likely endometriosis in the majority of cases (Fig. 2.1). If so, then this would constitute one of the most colossal mass misdiagnoses in human history, one that over the centuries has subjected women to murder, madhouses, and lives of unremitting physical, social, and psychological pain. The number of lives that may have been affected by such centuries-long misdiagnoses is staggering to consider, likely involving figures in the multiple millions.

Fig. 2.1 Replica of Sigmund Freud's couch, where patients presenting with endometriosis-like symptoms were often diagnosed with hysteria. (Reproduced courtesy of Konstantin Binder, photograph from the Freud Museum in London.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Methodologies

A broadly defined subject such as pelvic pain is naturally bound to yield results mired in inescapable ambiguity, especially because conditions like appendicitis, nonendometriotic ovarian cysts, infections, and leiomyomas can produce similar gynecologic symptoms [2]. However, after filtering all histories through the lens of modern understandings, we feel confident that the following analyses include only those patterns of illness that share significant correspondence to current clinical interpretations of endometriosis.

For our research methodology, we pursued several strategies, including traditional searches of the PubMed/ Medline databases. Additionally, archival research was performed at several locations including the National Library of Medicine in Bethesda, Maryland; the Lane and Green libraries at Stanford University in California; and the medical history library of the University of California at San Francisco.

In some cases, it was necessary to translate primary sources that were available only in Latin. For this specialized task, we consulted with the Cambridge-educated Latin and Greek scholar, J. R. T. Holland of Quintus Latin Translation Service, whose expertise in translating medical texts from premodern eras proved especially crucial for demystifying several contested areas of the history of endometriosis.

Newly digitized medical literature made available by Google Books also proved to be a surprisingly useful new source. To achieve an interdisciplinary perspective, we also referenced a wide range of material from outside of medicine, drawing from the disciplines of psychology, literature, art history, and medical anthropology. Given the allegorical nature of many these alternative sources, they were not evaluated in the same manner as the medical literature intended to represent empirical experiences. Rather, their utility lies in their unique ability to convey otherwise nearly imperceptible cultural undertones, the prisms through which illnesses are invariably experienced and conceptualized.

With thousands of conceivable sources from which to choose, this brief survey should in no way be considered an exhaustive study. Nevertheless, we believe it fills a gap in the literature by providing a multidisciplinary historical analysis of endometriosis as it may have been conceptualized before its 1860 microscopic discovery by Rokitansky. We first presented the preliminary results of this research in March 2011, at the World Endometriosis Symposium held in Atlanta, Georgia.

The Search Begins

Historical representations of pelvic pain: Oxford's Bodleian Library MS Ashmole 399 We began our analysis by focusing first on the broadest category under consideration: historical representations of pelvic pain in women. As it turned

out, this subject proved rather elusive, one curiously and consistently neglected in the archives of history. Detailed accounts of menstrual pain in particular were rarely, if ever, chronicled. Yet the hundreds of medicants for gynecologic ailments listed in the various *Materia Medicas* throughout the ages provide in themselves a strikingly different account, articulating by proxy stories of illness that belie those found in mainstream medical literature.

It was by tracing these nearly imperceptible leads that we eventually stumbled upon a late thirteenth-century medical manuscript, referred to as MS Ashmole 399 (folios 33–34) in which images of a woman apparently doubled over in pain can be found [3] (Fig. 2.2). Although there are no texts to accompany the original drawings, experts believe the imagery represents a woman suffering from what was usually called at the time "strangulation or suffocation of the womb." The linguistic lineages of these terms are still contested, but many scholars believe their roots can be traced to the *hysterikos-hysterike pnix* family of disorders, loosely defined disease frameworks formulated by Hippocratic and other Greco-Roman authorities throughout Classical and Late Antiquity, and the original source of the word being *hysteria* [4–7].

Fig. 2.2 Experts on medieval medicine describe this late thirteenth-century image from a medical textbook as one depicting a case of uterine suffocation, a disease profile with many similarities to endometriosis. (Reproduced with permission of Oxford University, Bodleian Library, MS Ashmole 399, f. 33–34.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Classical and Late Antiquity

The Animalistic Womb

Although strangulation or suffocation of the womb took on many contradictory meanings throughout history, their earliest antecedents may have stemmed from concepts first posited by the ancient Egyptians as long ago as 1855 BC. However, they were later popularized by the Hippocratic texts, Plato, and other Greco-Roman sources of Classical Antiquity [8] (Fig. 2.3). The basic concept underlying these disorders rested on the premise that the uterus was not actually a regular organ, but rather one more analogous to a live animal, hungry for motherhood.

Though a metaphorical rather than literal analogy may have been intended, the idea of the animalistic womb eventually began informing everyday practices. From this pretext emerged one of ancient medicine's most enduring dogmas, the idea that if a woman did not fulfill the socially proscribed roles of marriage and motherhood, her uterus would be deprived of its intended purpose. From this presumed unnatural state, it was believed that the uterus would begin to wander about—the famous wandering womb—and thus contribute to the onset of all manner of illness [5, 7, 9–14]. The notion of a wandering womb naturally strikes a modern audience as an anatomic impossibility. Yet it suggests a causal connection with pregnancy that is nearly identical to a modern assumption about endometriosis: The idea that pregnancy can temporarily suppress symptoms.

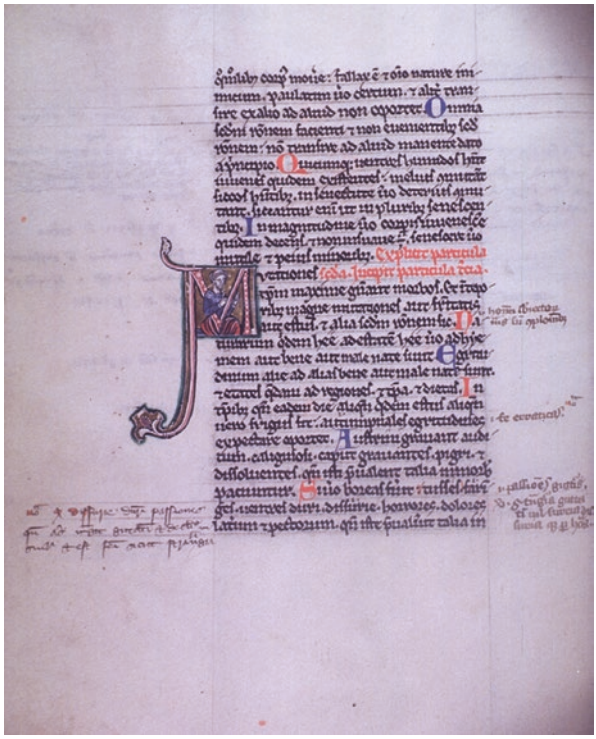


Fig. 2.3 In the Hippocratic Corpus, several gynecological symptoms are mentioned, which bear striking similarity to those of endometriosis, including uterine ulcers, adhesions, and infertility. (Page of text in "Aphorismi" with an illuminated small "M," Record UI. 1014450- 55, In: Hunayn ibn-Ishaq al-'Ibadi, Oxford, thirteenth century, l. 19v, Isagoge and other medical texts, Census 78. Reproduced courtesy of the U.S. National Library of Medicine.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

The Hippocratic Corpus

These theories inform many of the medical practices described in the Hippocratic corpus, a compilation of works written by various authors throughout the fifth through fourth centuries BC. The translations of these Hippocratic texts have been the subject of academic debate for centuries. However, after consulting numerous sources, we identified several relatively unambiguous disease profiles that allude to the wandering womb and other symptoms suggestive of endometriosis. The correlations become particularly evident when we learn that the Hippocratics viewed the following four factors as highly predictive of gynecologic disease: (1) menstrual dysfunction is a cause of disease, (2) pregnancy is a possible cure, and (3–4) pain and infertility as potential outcomes if the woman is left untreated [7]. Nearly 2500 years have passed since these observations were made, yet remarkably they correspond nearly seamlessly to the set of symptoms identified today as emblems of endometriosis. It is unfathomable that such uncanny correlations could remain suspended in a timeless stasis for so long. But what is even more incomprehensible is how such a uniquely patterned symptom profile could exist for ages without others realizing it was the hallmark of a distinct disease.

It was most likely the endless upheavals of medieval times that left such crucial Hippocratic insights buried in the debris of history. This is the most plausible explanation because, as we will see, these four core assumptions would inform essentially all Greco-Roman ideas of why gynecological disorders arise up until about the fifth century AD, the period many mark as the beginning of the European Middle Ages.

The Hippocratic texts provide many examples of how these four core concepts not only influenced ancient diagnostics and prognostics but also closely paralleled modern views. For example, in a near conceptual equivalent to the twentieth-century notion of endometriosis as a "career woman's disease," the Hippocratics suggested that delaying motherhood could trigger disorders of the uterus, with painful menstruation cited as one such outcome.

Women who suffered from dysmenorrhea were therefore urged to marry and conceive as quickly as possible [15].

Other dire consequences were predicted for those who failed to partake in the pregnancy prescription. One Hippocratic author warned that "if they have never been pregnant, the deranged state of menstruation is more common and more dangerous than when they have borne children" (a paraphrase by the translator) and that she will be "release[d] from this disease, when she is pregnant" [4, 7].

Childlessness in older, married women (i.e., cases of presumed infertility) was recognized as another predisposing factor for gynecologic disorders [4]. Drawing from the same pregnancy-as-therapy orthodoxy, another group believed to be particularly susceptible to gynecologic disorders was presumably fertile women who nevertheless remained childless; young widows and virgins who had already menstruated but remained unmarried typified this category of susceptible females [4, 16].

Detailed reports of menstrual disorders Detailed accounts of other menstruation-related disorders were reported in a chapter titled "Aphorisms," in which the Hippocratic author describes menorrhagia as a potential cause for pathology [16] and proclaims: "When the menses are excessive, diseases take place" [17]. It was also observed that in some women their "floodings," an archaic term for menstruation, were followed by "grumulous clots … accompanied with pain, inflammation of the uterus, [and] hysteric paroxysms." Additionally, in the Hippocratic chapter titled "Diseases of Young Girls" (translated less accurately today as "Virgins"), the authors observed that "the menses sometimes suddenly appear abundantly at the end of 3 months, in clots of black blood, resembling flesh; sometimes ulcers of the uterus ensue, requiring much attention" [16]. The Hippocratic author goes on to report: "When in a diseased state, the menses are of a bilious character; they have a black and shining appearance … and are accompanied with an erratic fever, chills, nausea, and heartburn." Allusions to perhaps bowel or lung endometriosis are also evident in the observation that "sometimes the menses are vicariously discharged by vomiting or stool; more commonly is the case with virgins than with married women."

Uterine adhesions and ulcers In the chapter "On the Nature of Women," we learn that the Hippocratics were also familiar with uterine adhesions. As the translator of these texts explained, they advised that "in case of adhesions between the uterus and other parts, indurations, suppuration of the womb, and ulcers, sometimes arise, or discharges which prove fatal if not attended to; fomentations of urine are among the measures recommended. The usual effect of this state is said to be sterility" [16]. Some of these translations are still the subject of heated academic debates, particularly the term "hysteric paroxysms." Yet based on the textual evidence in its entirety, it is at least reasonable to surmise that these Hippocratic physicians may have been encountering endometriosis.

Medical therapies The types of therapeutic options available were generally ingestible concoctions, fumigants, or suppositories that contained such substances as the urine of men or bulls, tar water, chaste tree (*Vitex agnuscastus*), pomegranates, cantharides, or castor oil (Figs. 2.4, 2.5, and 2.6). In analyzing the histories of these individual substances, we came across some surprising results. The medicinal usage of cantharides, for example, has an especially colorful history; although it is actually derived from dried beetles, throughout history it came to be known as the infamous aphrodisiac "Spanish fly."

Pomegranates and chaste tree also were deployed for centuries as contraceptives and treatments for menstrual disorders. Known as *shíliu* in Chinese, the pomegranate has been traditionally viewed in China as a source and symbol of fertility [18]. Recent studies have even begun to analyze its purported antiproliferative and antiaromatase properties [19].

In contrast, the pine resin-derived nostrum known as tar water was practically incompatible with life [20]. The same foul substance Charles Dicken's character Pip

Fig. 2.4 Allegorical image of fumigation, as depicted in John Collier's painting "Priestess of Delphi," 1893. (Reproduced with permission of the Art Gallery of South Australia, Adelaide.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.5 *Lytta vesicatoria,* known in modern times as the aphrodisiac Spanish fly, was one of many pharmaceuticals prescribed in the Hippocratic Corpus for treating menstrual disorders and infertility. (Reproduced courtesy of Christophe Franco, http://en.wikipedia.org/wiki/File:Lytta-vesicatoria.jpg.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.6 Recent studies have begun to analyze the purported antiproliferative and antiaromatase properties of pomegranates, prescribed for fertility and menstrual disorders in both Hippocratic Medicine and ancient Chinese medicine. (Reproduced courtesy of Benjamin Trovato, http://en.wikipedia.org/wiki/File:PomegranateChina.jpg.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

was forced to ingest as punishment, tar water was considered by the Hippocratics as so effective (or so odious) that women of antiquity were warned they would be "barren forever" if they ingested it [20, 21]. Fragments of this belief appear to have been handed down over time because today some veterinarian studies have shown pine extracts to exert modest antifertility effects in animal models [22, 23].

As for the use of urine for medicinal purposes, in modern gynecology, we are no doubt familiar with the use of pregnant mare urine extracts as Premarin's main ingredient. What is less clear is whether the ancients would have been capable of extracting similar hormone-disrupting constituents from the urine of bulls or men. The literature provides few examples of well-designed, peer-reviewed studies in humans, but several animal studies do suggest that bull urine can exert antiestrogenic properties in mice [24].

Other more inventive therapies were explored as well. One of the most unusual therapies was the practice of succession. Designed as a mechanical means for

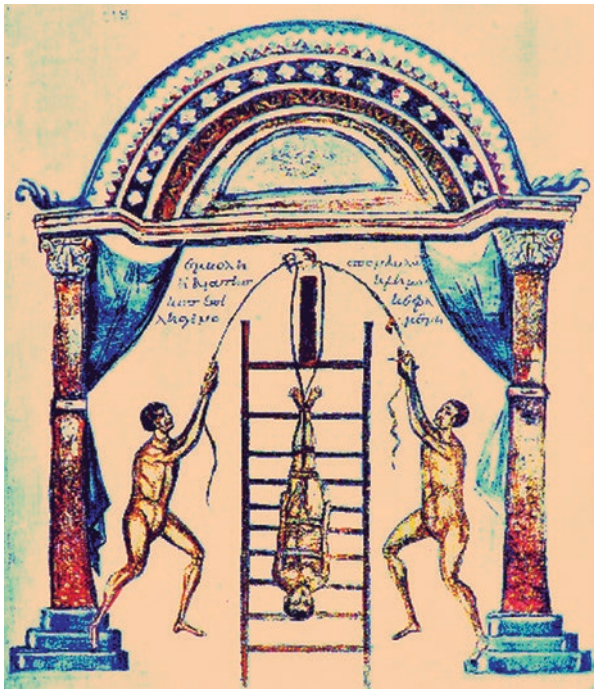


Fig. 2.7 Uterine suffocation, vaginal prolapse, and other gynecologic conditions were sometimes treated with succussion, the ancient Greek practice in which patients are bound to a ladder, turned upside down, and shaken vigorously, with the idea being that the uterus would be shaken back into its proper position. (Reproduced courtesy of BioMed Central Ltd and SpringerImages. Scoliosis 2009;4:6. Image from the illustrated comments of Apollonius of Kitium on the Hippocratic treatise *On Articulations*. Bibliotheca Medica Laurenziana, Florence.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

repositioning the uterus, a session of succussion involved tying the patient to a ladder, which would then be turned upside down and shaken up and down until the womb returned to its rightful place [25] (Fig. 2.7). In this case, visibly prolapsed uteri were most likely the intended target, making the practice infinitely more comprehensible from a modern standpoint.

Admittedly our analyses of ancient pharmacology are speculative at best, given the absence of high-quality evidence to support these theories. As Renckens argues so effectively in his article about alternative treatments in reproductive medicine, much of the existing evidence appears to be woefully inadequate [26]. Even so, further investigations may be warranted. As reported in a recent editorial by endometriosis expert, Dr. Linda Giudice [2], preliminary studies suggest that: "Chinese herbal therapies have exhibited antiproliferative, antinociceptive, and prosedative properties, as well as anti-inflammatory actions, antioxidant characteristics, suppression of COX-2 and cytokines, and mechanisms involved in the cytokine response, such as inhibition of NF-KB" [19, 22–24, 27].

"Extremest anguish" Although we do not usually think of the acclaimed philosopher Plato (375 BC) as being involved in medicine, this did not stop him from expressing his own opinions about gynecologic disorders. In fact, Plato was actually among the first to mention the extreme pain that women suffered as a result *suffocation of the womb*. He explained that the disorder is triggered when "the womb remains barren too long after puberty, is distressed and sorely disturbed, and,

straying about the body and cutting off the passages of breath, it impedes respiration and brings the sufferer into the extremest anguish and provokes all manner of illness besides" [28, 29].

By the time Roman scholar Pliny the Elder (23–79 $_{AD}$) began reporting on suffocation of the womb, several new observations had been added to the diagnostic profile. Included among these was an account of the disorder's peculiar ability to reduce women to some sort of semiconscious state, lying "as if dead for seven days" [7].

Soranus

Inflammation of the uterus About a century later, Soranus (ca. 98–138 $_{AD}$) reported similar findings, but offered critical new clinical insights when he explained that women were falling unconscious as a result of the disorder's characteristic violent uterine contractions, which Soranus observed could manifest in either chronic or acute forms [7] (Fig. 2.8). To explain these symptoms, Soranus departed from tradition by becoming the first to suggest inflammation of the uterus as part of his radical new theory about the origins of suffocation of the womb.

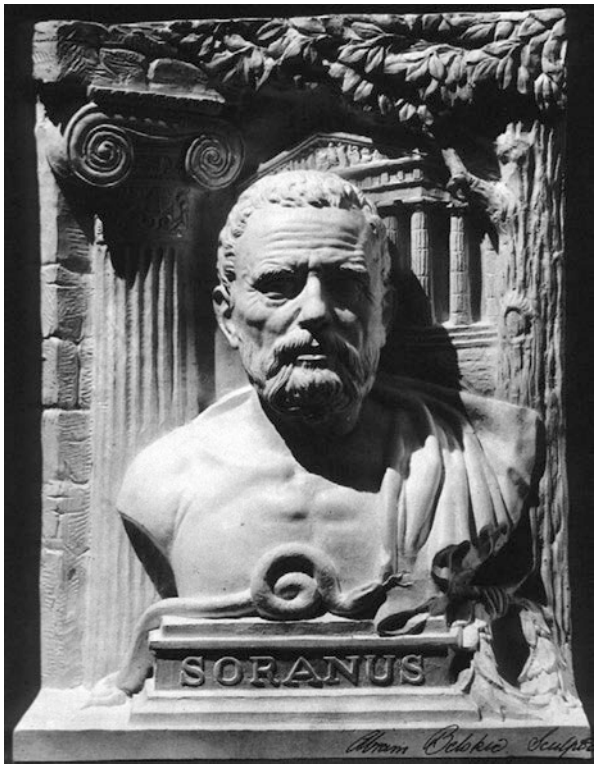


Fig. 2.8 Soranus of Ephesus (circa 98–138 $_{AD}$) described many endometriosis-like symptoms, including menstrual disorders that led to infertility and cases of uterine suffocation that caused violent uterine contractions. (Reproduced courtesy of the U.S. National Library of Medicine; Portrait no. 6313-A.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

More than just an essential new theoretical framework, Soranus's detailed macroscopic knowledge of these and other uterine pathologies supports the idea that human autopsies may have informed his views. Although Soranus admitted to having performed autopsies, they would have been considered highly unorthodox and somewhat risky for the times. Indeed, unassuming as this revelation may seem, Soranus's accurate anatomic descriptions of the uterus actually call into question other historical accounts that claim human dissections had been all but abandoned by that time.

As for those susceptible to uterine disorders, Soranus reports that the conventional views of his day were that "many women, menstruating with difficulty and pain because of a long widowhood, have menstruated freely after marrying again," with marriage implying that the conception curative would soon follow [15, 30]. In another chapter, Soranus revisits the topic from a different angle, explaining again that many physicians view pregnancy as healthful because it was believed that "some women, menstruating with difficulty and suffering uterine pressure, have been freed of their troubles after pregnancy" [15].

Other symptoms Investigating the other symptoms ascribed over the years to suffocation of the womb is a complicated matter. Yet after careful evaluation of research by several scholars specializing in women's ancient medicine, we rounded up all the disparate descriptive evidence and found that convulsions, epileptic-like "fits," abdominal pain, nausea, vomiting, digestive disorders, gritting of the teeth, excessive perspiration, palpitations, ashen skin, and the appearance of lumps near the abdominal sidewalls were all among the most commonly cited symptoms [5, 9, 10, 12]. The observation of lumps appearing to the side of the uterus was a symptom that piqued our interest considerably, but several insurmountable translational ambiguities made it quite difficult to extract any additional insight about this particular description.

Convulsive symptoms as part of gynecologic medicine represent another intriguing challenge to our modern conceptions of diagnostic criteria. As it turned out, the original meaning of hysterical convulsions, during this era, generally referred to women falling to the ground, doubled over into a fetal position. Such descriptions correspond well to the images found in the MS Ashmole 399 drawings, and they could very easily be describing a response to acute abdominal pain [5].

Celsus

Reports of women suffering from convulsions and/or epileptic-like symptoms in association with suffocation of the womb continued to be mentioned by the next generation of medical scientists. Roman scholar Celsus described women suffering from "violent" illness coming from the womb, who fall down as if suffering from epilepsy. However, "rather than exhibiting the normal signs associated with that disorder, such as foaming or eyes rolling back, instead [they] lie down as if in sleep" (Fig. 2.9).

Fig. 2.9 Second-century Greek encyclopedist Celsus (circa 25 $_{BC}$–circa 50), described cases of a violent uterine illness that caused women to fall to the ground, convulsing and fainting from attacks of acute pain. (Reproduced courtesy of the U.S. National Library of Medicine, Portrait No. B04927, titled "A. C. Celse" by Pierre Roch Vigneron, Paris, 1865.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Of particular note, Celsus reports that, in some cases, the disease returned frequently and that "some women suffer from this their entire lives" [4, 7, 29]. This specific observation proves especially relevant in view of our current historical study of endometriosis, but it was Celsus's reports alluding to violent fits of the womb that seemed to attract the most attention throughout the ages. Some scholars even have suggested that Celsus's comment was the original source behind the term "hysteric fits."

Despite both the Hippocratics' and Celsus's unambiguous explications of a gynecologic disorder distinct from regular epilepsy, over the years, the boundaries separating the two disorders became more diffuse, leading to a continued conflation of epileptic fits with hysteric fits. This practice would later figure into a series of rather curious theories that developed about women and illness in subsequent eras [31].

Dioscorides

Just a few decades after Celsus, one of the most celebrated physicians of Late Antiquity emerged, the Greek physician Pedanius Dioscorides. His *De Materia Medica* (ca. 77 $_{AD}$) stood for ages as one of the most influential ancient treatises in Western medicine, "the chief source for herbalists of all nations" and compulsory reading in medical education for more than 15 centuries [32, 33] (Fig. 2.10).

Fig. 2.10 In Greek physician Pedanius Dioscorides's acclaimed work, *De materia medica* (circa 77 $_{AD}$), uterine suffocation is described as a menstrual disorder with many parallels to endometriosis. (Reproduced courtesy of the U.S. National Library of Medicine, Portrait No. 1550.3, anonymous work titled "Dioscorides Pedanius of Anazarbos."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Dioscorides's text differs from others reviewed so far in that it is organized in an encyclopedic format. Enumerating nearly 1000 pharmacologic compounds in a descriptive manner, though without commentary on presumed etiologies, the encyclopedic organization can be disorienting. However, it reflects the best pharmacologic science of the day, offering an informative narrative about first-century medical practices and furnishing some insight into gynecologic disorders as they were understood and treated nearly 2000 years ago.

Pain and collapse Though the theoretical continuity concerning uterine suffocation is clearly evident in *De Materia Medica*, Dioscorides still provides fresh new perspectives about menstrual dysfunction and a uterine disorder named "strangulation of the uterus," which exhibits the same tendency as suffocation of the uterus to render women unconscious. Like his predecessors, Dioscorides describes a disorder that causes women to suddenly fall down, apparently hovering either in some sort of quasi-conscious state or in an otherwise diminished condition that renders them unable to raise themselves to a standing position. As noted before, many of these signs could signify responses to acute attacks of pain. That the afflicted women are lying down in some fashion can be established by a prescription for shellfish shells that is believed to help "rayse up such women as are troubled with strangulatus uteri, & such as have ye falling sicknesse" [32].

Medication Views about menstrual disorders were surprisingly advanced, with Dioscorides clearly acknowledging menstrual pain as an organic, pathologic condition requiring medication, something that even some twenty-first-century physicians fail to recognize at times. As for medicinal substances, the inventory abounds with prescriptions for such items as bed bugs, brains, human urine, and other decidedly indelectable morsels. We will spare the reader these details and offer instead excerpts of the least odious medical therapies, one of which is a dysmenorrhea treatment described as "the horne of an Hart being burnt & washt, if it be dranck the quantitie of twoe spoonfuls … It is good also for women troubled with ye flux (of ye wombe) being given with somme liquor fitting for that grief" [32].

As for Dioscorides's references to "women troubled with ye flux," naturally many so-called troubles aside from dysmenorrhea could be correlated with menstruation, such as amenorrhea, anemia, or menorrhagia. However, based on evidence derived from other passages, it appears that Dioscorides was likely referring specifically to menstrual pain and the other symptoms associated with strangulation of the uterus. Further evidence substantiating this view can be inferred by the fact that those other menstrual disorders were assigned their own distinctive remedies.

Menstruation suppression Dioscorides's work is remarkable for another reason, as it appears to be the first of its era to mention in unequivocal terms medications designed to suppress menstruation. Like the Hippocratics 500 years earlier, it demonstrates that Dioscorides recognized menorrhagia not only as a distinct menstrual variation but as a potentially pathologic disorder in need of medical intervention [32]. For this ailment, Dioscorides suggested that the brain of a hare, "being dranck after three dayes after ye menstrual courses," is reported to cause sterility; likewise, it stops the "flux of ye wombe and of the belly" [30, 32].

This was a particularly interesting discovery because many historians specializing in women's medicine of antiquity have reported nearly exclusively on medicants prescribed for *inducing* menstruation, putatively for cases of amenorrhea but that many believe were actually intended as abortive agents. Without this critical insight offered by Dioscorides, the ancient world, as interpreted in modern times, would appear to be one either nearly devoid of any menstrual disorders other than amenorrhea or rife with epidemic abortive practices.

As mentioned before, naturally a retrospective evaluation of the efficacy of these substances is impossible. In any case, the majority of modern biochemical studies that attempted to measure the efficacy of ancient pharmacologic substances have proved inconclusive at best. However, a few studies using animal or in vitro models have pointed to possible minute traces of hormone-disrupting agents in medicants believed to have been used in antiquity [34–37].

Regarding Dioscorides's prescription for the horn of a hart to treat menstrual ailments, our research found that "hart" was the British name for a male stag of the red deer species common throughout Europe and Asia Minor [38]. In traditional Chinese medicine, red deer antler has been used to treat male impotence and gynecologic disorders in women [2]. A recent animal study from an alternative medicine journal

even suggests that some antler velvet products may "produce anti-inflammatory compounds that assist in the regulation of prostaglandins" [39].

Another modern study found that, of several medicinal herbs believed to have been used since antiquity, "20 showed strong and 10 weak anti-oestrogenic activity." Among those found to have strong antiestrogenic activity was prunella vulgaris (commonly called Self-heal, or *Xioakucao* in Mandarin Chinese), an herb used in Hippocratic and traditional Chinese medicine for centuries to treat dysmenorrhea [34, 35]. Whatever the case, it is clear many of these ancient beliefs survived the journey through time, as red deer antler and other products touting hormone-altering properties are still offered today in alternative medicine.

Galen

Violent uterine contractions and inflamed ligaments Practicing medicine about a century or so after Dioscorides, Claudius Galen of Pergamon (129–216 $_{AD}$) had at his disposal more than 500 years of medical heritage concerning suffocation of the womb, a disease entity with a symptom profile that had remained stable for centuries [7] (Fig. 2.11). Although convulsions and fits continued to be the headline symptoms, Galen offered fresh new insights, including one of the clearest descriptions of symptoms suggestive of adhesions and/or endometriosis-infiltrated ligaments.

Galen provided these new clinical symptoms as part of his proposed theory of pathogenesis, which suggested that suffocation of the womb was triggered when the membranes that anchor the uterus in place became engorged as the result of excessive menstrual blood. Galen believed that this excessive pressure on the ligaments caused the membranes to thicken and stretch with tension, which in turn pulled the

Fig. 2.11 Claudius Galen of Pergamon (129–216 ACE), Roman physician of Greek heritage, described a gynecologic disorder that produced violent and painful uterine contractions and swollen and inflamed ligaments. (Reproduced courtesy of the U.S. National Library of Medicine, Call No. WZ 348 C25, no. 51 sol. Painting by Robert A. Thom [1952] titled "9. Galen—Experimenter in Compounding" [131–201 $_{AD}$].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

uterus into contorted positions. In turn, Galen surmised that these contortions were causing the painful and violent uterine contractions, lacerations, and inflammation from the repeated physical friction [7].

Aretaeus concurrence Aretaeus, a contemporary of Galen's, provided nearly identical descriptions, suggesting that the uterus's membranes underwent morphologic changes during menstruation, resulting in distending or contracting motions "like the sails of a ship" [7]. Allusions to violent symptoms and instances of unexpected deaths were beginning to be mentioned with greater frequency by this time. Aretaeus went on to describe suffocation of the womb as a condition triggered "when [the] womb moves upwards" and "presses violently on intestines"; it causes "exhaustion, loss of control of the knees, dizziness, … her limbs are weakened," and "it resembles epilepsy" [30, 40]. Expressing sentiments with uncanny parallels to modern concerns about productivity, Aretaeus even notes that, when the disorder is severe, there will be "hesitation in doing her tasks" [30, 40]. For those attacks that have an acute onset, Aretaeus advised that it was essential for a physician to be summoned quickly to prevent death, an outcome that Aretaeus considered unexpected and difficult to believe as the woman just moments before had not appeared so gravely ill [29].

Psychological factors In what may have been the first fateful moments when psychological elements began fusing more consistently with gynecology, Galen contributed another original if notorious observation. He made what appears to be one of the most explicit references associating uterine disorders with mental illness when he hypothesized that young widows, still viewed as particularly prone to uterine distress, could be "driven to madness as a result of their loss of sexual fulfillment" [41]. Although there were somewhat similar allusions made in earlier works, including the Hippocratic texts, Galen elaborated on these notions with such authority that his work may have been the catalyzing force responsible for ushering in a disturbing new era in women's medicine, when gynecologic ailments first began to be conceptualized as psychological in nature. As subtle as this theoretical shift may at first appear, its repercussions would prove boundless, rippling through the very core of social and scientific beliefs for centuries.

Final Thoughts

With young girls who had begun menstruating considered particularly vulnerable to gynecologic dysfunctions and pregnancy considered a possible cure, Western medical authorities throughout Classical and Late Antiquity established the appropriate age of marriage as sometime within a year of menstruation, which was estimated to be approximately the ages of 14–15 during that period [4]. Had some of these cases actually been early observations of endometriosis, conception as a potential cure would have appeared quite efficacious. After all, women during this era usually began conceiving in their teens and raised an average of five to six children, though

probably experienced even more pregnancies due to the high rate of infant and child mortality. Meanwhile, with breastfeeding lasting up to the age of 2 years for each child, these culturally normative behaviors could have functioned as a natural suppressant of the disorder (if it was endometriosis). Therefore, many successive years of childbearing could have indeed made it appear to have been cured [4].

When one considers that suffocation/strangulation of the womb was also believed to be triggered by what was called "spoiled menstrual blood" or "spoiled seed"—in other words, another association with menstruation—then the notion that these ancient physicians may have been witnessing some cases of endometriosis is all the more plausible [5].

Translation ambiguity. Compelling though these historical vignettes may be, we are obliged to mention the many inevitable shortcomings of these investigations. To begin with, it is well known that analyzing ancient texts with the intention of importing meaning back into a modern context is an endeavor fraught with unavoidable translational and cultural misinterpretations. Thus, the resulting analyses may be more conjectural than conclusive. That most English translations available to us today have undergone a linguistic journey from Greek to Syriac to Arabic to Latin to English is just one example of how easily the original meanings could have been distorted. Complicating matters further is the fact that many of the ancient texts were derivative works, passed down as nearly verbatim transcriptions of previous publications. This means that one can never be entirely certain whether ancient authors were reporting their own independently obtained observations or were simply presenting the clinical experiences of others as their own. Of course, today such practices are considered the ultimate in scientific sacrilege.

Naturally, the various symptoms described could also apply to dozens of other disorders. The contorting spasms, for example, could have been caused by tetanus, thought to have been somewhat prevalent in those time frames and geographies [30]. As admitted from the outset, without histopathologic confirmations, concrete conclusions cannot be made. Yet when viewing the textual evidence in its totality, it is fair to assume that at least some of these cases could have been unwitting early descriptions of endometriosis, even despite some areas of ambiguity. Overall, the preponderance of evidence gives reason for pause. It is clear that the *hysterikos* family of disorders was to some degree a veritable diagnostic junk drawer. However, the continuity of core assumptions—such as viewing pregnancy as a potential cure for painful menstruation—which occurred in concert with the equally suggestive symptoms of vomiting, "violent pain coming from the womb," and painful, blood-filled membranes serves as credible evidence that we are witnessing the formative outlines of a distinct disease paradigm edging into existence [7].

The Middle Ages

As epochs go, the European medieval era—the so-called Dark Ages—is often conceptualized as though it were one vast expanse of scientific and cultural stagnation. Considering that Europe was ravaged by a succession of falling empires, wars,

Fig. 2.12 The reintroduction of supernatural disease etiologies in Western medicine occurred most dramatically during the Middle Ages, when pandemics like the plague wiped out an estimated 30% to 60% of Europe's population. It was during this time that uterine suffocation began to be misconstrued as the work of witchcraft or demonic possession. (Reproduced with permission of the British Library Board (C), Record Number: c6541-07, Shelfmark: Royal 6 E. VI; Page Folio Number: f.301: Plague victims etching by James le Palmer, titled "*Omne Bonum*."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

plagues, and pestilence, it is easy to see how such impressions were formed, especially when compared with the grand luminosity that had been Greco-Roman medicine and that was now evident in the scientific renaissances that were occurring in Asian centers [42] (Figs. 2.12 and 2.13). Indeed, progress in European medicine seemed to grind to a screeching halt. Some experts have characterized this stagnation as a period spanning 900 years, from about the fifth through thirteenth centuries.

Early Middle Ages (Fifth to Eleventh Centuries AD)

Supernatural versus superscientific In the apparent scientific void of the Middle Ages, theological and supernatural influences returned to the forefront of the popular imagination. Such beliefs competed alongside and at times edged out much of the hard-won scientific heritage that had been so meticulously synthesized throughout antiquity. It did not help that such revered scholars as Lactantius (4th $_{AD}$) questioned the need for any further scientific inquiry, asking, "What purpose does knowledge serve … what blessing is there for me if I should know where the Nile

Fig. 2.13 The widespread devastation caused by the plague was followed by unprecedented religious, social, and economic upheavals that profoundly affected the course of European history. (Reproduced courtesy of the U.S. National Library of Medicine, "Epidemics Die Pest, Plague scene" [Plague victims in city square], Call No. WA 100 C25 No. 6 box 12 sub.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

rises, or whatever else under the heavens the 'scientists' rave about?" [42]. In such an environment, miraculous cures and demonic possessions alike became plausible theories to explain health and sickness. As one historian described it, "illness metaphors were those of sin" or were invoked "as a salutary tool to scare people straight, with visions of hell dragged out for special effect" [42] (Fig. 2.14).

As we will see, these developments somehow insinuated themselves into the outer edges of women's medicine, becoming the theoretical backdrop from which both social and scientific views concerning women and illness were sometimes formed. These distinct ideologic shifts were exemplified well by the views of Greek physician Paul of Aegina (625–690 AD), who suggested that suffocation of the womb was an illness that usually afflicted "lascivious" women, or "those who use drugs to prevent conception" [7].

Almost as if in lockstep with the changing attitudes about sickness, treatments appeared to become noticeably harsher. For example, Oribasius (325–397 $_{AD}$) suggested a shouting therapy as a means for reviving those who had passed out from suffocation of the womb [7]. While the shouting treatment in itself is a powerful testament to the ideologic trends on the rise, it also demonstrates that uterine suffocation was still causing women to pass out, the same observation made by the Hippocratics nearly 900 years earlier.

Fig. 2.14 Throughout the Middle Ages many continued to view hysteria or other misunderstood disorders as signs of witchcraft or demonic possession, a charge that would have subjected women to a range of punishments and/or treatments, including executions, exile, or, as is depicted in this etching, exorcisms by a religious leader. (Reproduced courtesy of the U.S. National Library of Medicine. A priest healing a possessed woman, from *Histoire prodigieuses et memorables, extraictes de plusieurs fameux aureurs, Grecs, & Latins,* artist Pierre Boaistuau, ca. 1566. Paris: Gabriel Buon, 1598, p. 1272, Record UI No. 101435552.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Exotic notions such as shouting therapy and hungry lascivious wombs naturally have taken center stage in historical reviews, but it is important to note that medieval physicians did achieve several important clinical discoveries. For example, under the broad category of uterine suffocation or hysterical convulsions, Paul of Aegina did describe other potential symptoms such as abscesses or ulcers of the uterus that could burst open: "when the ulcer is spreading, the discharge is fetid, black, attended with great pains, and other symptoms of inflammation" [20].

Aëtius of Amida Other achievements made it clear that all was not lost in terms of medical progress. In fact, two of the most crucial conceptual breakthroughs to date were achieved at this time by Aëtius of Amida (502–575 $_{AD}$), who became one of the first to suggest more explicitly that suffocation of the womb was predominantly triggered by menstruation. Similar to Galen, Aetius surmised that the convulsive symptoms observed in those with suffocation of the womb were actually the result of painful uterine contractions. As for the root cause of such violent uterine contractions, Aetius suggested they occurred as a result of the "cooling of the uterus during menstruation" [29].

Alas, such breathtaking breakthroughs were often followed by spectacular reversals. Within a few centuries of Aetius, a most unfortunate addition to treatment practices was introduced: choking the necks of women suffering from uterine suffocation. This "therapy" was believed to induce the womb to return to its rightful place [7]. Indeed, such discordant developments—characterized by soaring highs and perilous lows—would epitomize the next several hundred years of European medicine.

China and the Near East While developmental dissonance ensued in Europe, Asian countries stood in contrast as flourishing centers of medical and scientific innovation. Many historians have described Babylon and China of the ninth century as leading the world intellectually. It was in these Asian centers that the hospital was invented, the concept of zero was refined, and *al-jabr*—algebra—was developed to exquisite perfection [42] (Figs. 2.15 and 2.16).

Arabic, Persian, and Muslim science Arabic Medicine, which many believe is more correctly described as Muslim medicine, was especially progressive. Its cultural emphasis on scholarship meant that Muslim scholars were among the first to rediscover and commission the translation of thousands of Greek and Roman medical texts [30], which would prove a crucial factor in the rebirth of scientific inquiry that later revolutionized European societies. Physicians played a vital role in these translational efforts, including three of the most esteemed of the era: Persian physicians Haly Abbas (?–994), Avicenna (980–1037), and Rhazes (865–925). As many

Fig. 2.15 While European centers were descending into the so-called dark ages, Asian and Middle Eastern centers of science and medicine were on the ascent. (Reproduced with permission of the Wellcome Library, London. Image no. L0034735, Woodcut from *Tong ren shu xue zhen jiu tu jing* [Illustrated Manual of Acupoints on the Bronze Man] by Wang Weiyi, published in 1443; Illustrating methods of locating the *gaohuang* [vital region] point. Library of Zhongguo zhongyi yanjiu yuan [China Academy for Traditional Chinese Medicine].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.16 Textbook pages from acclaimed third-century Persian physician, Ali al-Husayn ibn Sina, better known in the west as Avicenna (980–1037). (Reproduced courtesy of U.S. National Library of Medicine, call no. WZ 56 C24 no. 3-d box 21 sub.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

of the medical theories arising out of this era shared a great deal in common with those promulgated by the Greco-Roman scholars of antiquity, few new insights into uterine suffocation were made. However, this new generation of medical scientists did isolate and discover dozens of new medicinals that were unknown to Europeans, including colchicum, camphor, senna, nutmeg, cloves, and alcohol-based concoctions, all of which would become essential new pharmaceuticals in Western medicine throughout and beyond the Middle Ages [43].

Another achievement of note was made by Avicenna, who reconceptualized pain as a biologic condition that was completely at odds with nature and without any conceivable medical benefit [43]. In the wake of these influential new ideas, many conventional views about pain were called into question, especially those that assumed it to be beneficial for hastening healing or worse, a karmic payback for past misdeeds. Although these theoretical musings about pain may seem peripheral to the story of endometriosis, such efforts to decode its biological basis would eventually prove to be of central importance. Overall, with their abiding commitment to scholarship and scientific investigation, Muslim medical practitioners proved to be the critical catalyst for reinvigorating medicine in Asian centers, and eventually throughout Europe.

High Middle Ages (Twelfth toThirteenth Centuries AD)

Twelfth century One of the earliest European centers to symbolize this scientific reawakening was Salerno, Italy. It was from Salerno that one of the era's best-known medieval gynecology manuals was published by the female physician Trotula (Fig. 2.17). Although the Trotulan text offers many unique insights into twelfth-century medicine, what is most impressive is that its portrayals of uterine suffocation continue to be essentially identical to those described by the Hippocratics nearly 15 centuries earlier. For example, as an extension perhaps to the Hippocratic experiments with bull urine, the Trotulan author mentions that an especially effective treatment for suffocation of the womb called for: "a powder be made of the testicles of a fox or a kid and that this be injected (into the vagina) by means of a tampon" [44].

As the renaissance spirit of Salerno suggested, the trend toward scientific medicine was clearly on the rise. Even so, saints, miraculous cures, and demonology continued to figure into the story of medicine. A curious amalgam of healing practices emerged, with the afflicted often seeking succor through traditional medical

Fig. 2.17 A page from a twelfth-century work attributed to Trotula, one of the most celebrated female physicians of ancient times, whose prescriptions for uterine suffocation included vaginal suppositories composed of ground goat gonads, among other ingredients. (Reproduced with permission of Wellcome Library, London.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

channels as well as through supplication to saints or designated temples of healing. It was within this milieu, when medicine reflected a peculiar mix of empirical, magical, and theologic elements, that the often bizarre pain behaviors of those seeking divine relief at public temples were sometimes construed as instances of demonic possession. Outlandish as these superstitions seem to our modern sensibilities, they were surprisingly enduring, persisting for several centuries with devastating consequences for women in particular [43].

The Renaissance: The Sixteenth Century

While not the most conducive environment for scientific progress, nevertheless by the sixteenth century, a new generation of medical pioneers achieved important milestones. Henri de Mondeville, called the Father of French surgery and surgeon to the king of France, challenged the long-standing belief that wounds needed to undergo suppuration in order to heal [43]. And what would one day prove beneficial to the story of endometriosis especially, by about 1250 autopsies had been reintroduced as a regular part of medical education in many parts of Europe, particularly Italy, France, and Germany [30].

Challenging Ancient Anatomic Assumptions

Organized university medicine also returned to Europe, with Padua and Bologna now among the era's leading centers of science and medicine. Within a few hundred years, the results of these educational innovations were clearly evident during the golden era of anatomy, when such pioneering anatomists as Vesalius and Gabriele Falloppio finally began challenging the edifices of ancient anatomic assumptions. Crashing sounds of an empire falling must have been reverberating across Europe as Vesalius sent Galen's five-lobed, blood-making liver and seven-segment sternums back to the midden heap of history (Figs. 2.18 and 2.19). There is even evidence to suggest that Vesalius may have studied suffocation of the womb (by this time also called hysteric fits). As one storyteller recounted,

> Vesalius, it is well known, had commenced dissecting a woman who had apparently died of an hysterical fit, when he perceived, on making the first incision, by her movements and cries, that she was still alive. The circumstance rendered him so odious in the sight of his fellow-countrymen, that he was forced to quit his native country and being shipwrecked on the coast of Spain, died of hunger [45].

Considering that many of Vesalius's own professors denounced him as "a madman whose pestilential teachings were poisoning Europe," it is possible that this story is more apocryphal than credible [46]. Of course, if true, it would surely have to count as one of the most spectacular misdiagnoses in history.

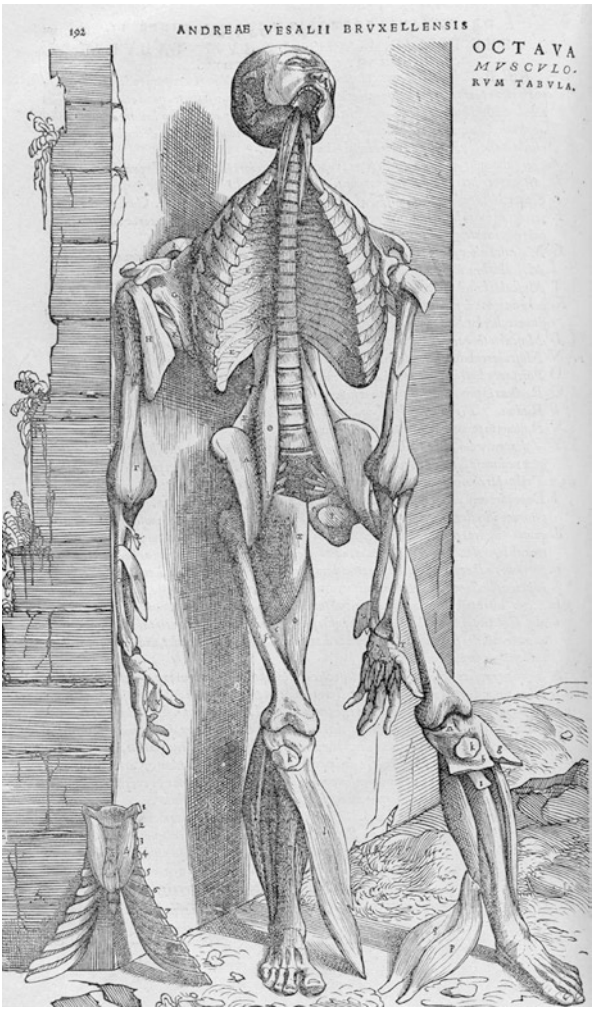


Fig. 2.18 Image from Andreas Vesalius's groundbreaking anatomy work, *De Humani Corporis Fabrica* (1543), which shattered thousands of years of assumptions about human anatomy. (Reproduced courtesy of the U.S. National Library of Medicine. Woodcut by Stephen van Calcar and the Workshop of Titian, Basel, 1543.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Medical bloodletting Even with Vesalius's purported monumental misstep nearly stealing the scene, it could not be denied that the Renaissance had indeed arrived. Some of the most dramatic religious, social, and scientific reforms in history occurred during this time, when questioning orthodoxy became a nearly universal mandate. Even patients, those hitherto strangely anonymous and presumed passive receptors of medicine, began to call into question traditional medical practices. This trend can be observed through the laments of one sixteenth-century physician, who wrote, "I am astonished by some, who will more willingly take 20 different drugs than endure one bloodletting that is necessary, given its great ease and simplicity. Drugs … [have] considerable drawbacks, not to mention the nausea, the upset stomach, and the severe intestinal cramps they usually bring about" [43].

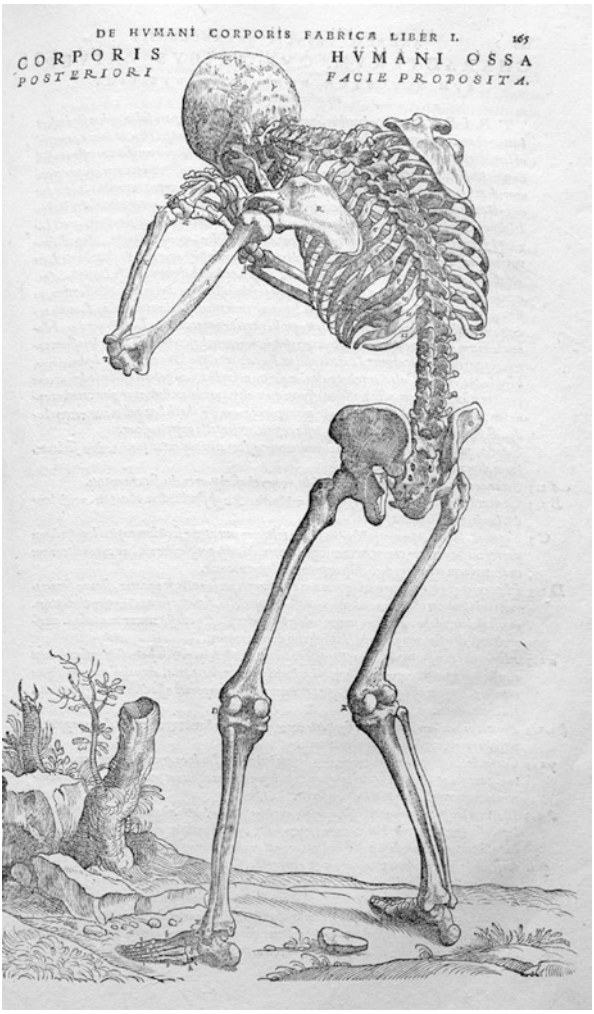


Fig. 2.19 Another image from Vesalius's *De Humani Corporis Fabrica*. (Reproduced courtesy of the U.S. National Library of Medicine; Call No. QS 11 C27 box 1 sub, Vesalius, Andreas, *De humani corporis fabrica,* p. 165 [Liber I], Basileae, Ex officina Joannis Oporini, 1543.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Ambroise Paré

As for progress toward understanding suffocation of the womb, by the sixteenth century, some of the era's most renowned medical authorities, such as William Harvey, Paracelsus, and Ambroise Paŕe, were explaining women's illnesses in etiologic terms that traced their heritage back to disease categories in existence for over 2000 years. By this time, suffocation/strangulation of the womb was also being referred to as hysteria, hysterik fits, or dysregulated vapors (vapours), which was a word used to connote menstruation.

In terms of women viewed as particularly susceptible to suffocation/strangulation of the womb, Ambroise Paŕe (1510–1590), France's leading physician of the

era and surgeon to four successive kings, offered essentially identical explanations to those found in the Hippocratic texts. However, Paŕe suggested that it was not just virgins and widows but also married women who abstained from sexual relations who were most often afflicted with the disorder [5, 47, 48].

Like Aetius from several centuries earlier, Paŕe suggested that menstrual vapors caused strangulation of the womb. Describing the attendant symptoms of menstrual vapors, Paŕe observed that women suffer from "strangulation of the womb … swlon or puffed up by reason of access of gross vapors and humors," leaving women "snatched as it were by a convulsive smotherion" [5]. The swollen uterus that Paŕe describes could correspond to general inflammation but also to symptoms of adenomyosis. Paŕe also noted that women suffering from suffocation/strangulation of the womb were in so much agony that they believed themselves to be "near death" [29].

Paŕe's observation that menstruation triggered the disorder again demonstrates that for centuries physicians had consistently observed several of the signature markings of endometriosis. Like Galen and Celsus, Paŕe also introduced the critical observation that the uterine ligaments were somehow involved in the illness, noting that the uterine "vessels and ligaments [are] distended with fullness" [29].

The Seventeenth Century

With medicine still hovering at the threshold between the old and the new, explanations of illness again reached an improbable apex. The pain symptoms associated with suffocation/strangulation of the womb began to be construed more frequently as a sign of demonic possession, madness, or witchcraft. However, illness depicted within a demonologic framework was not actually new. Ancient texts from various cultures had attributed demonic or otherwise supernatural causes to the condition of epilepsy especially [30]. Additionally, the idea that pain could mimic signs of madness had been considered throughout the ages, with many allusions made in medieval times of people driven mad by pain. At one point, pain was even called the "originator of madness" [7].

Organic, Mental, or Supernatural?

Demonic possession The convergence of these various theoretical elements found expression in Hendrick Hondius's engraving from 1642 called "Pilgrimage of the Epileptics to the Church at Molenbeek" (sometimes thought to be a depiction of dancing mania) (Fig. 2.20). The engraving shows a pilgrimage of women suffering from hysteria-associated epileptic-like symptoms on their annual journey to the renowned healing shrine of St. Vitus, viewed since "pagan times" as a source of miraculous cures, particularly for epileptic disorders. Legend had it that if one were

Fig. 2.20 Engraving from 1642 representing folkloric conceptions of women's illness, including hysteria and other disorders that may have been endometriosis or other gynecologic conditions. (Courtesy of the U.S. National Library of Medicine. Engraving by Hendrick Hondius, titled "Pilgrimage of the Epileptics to the Church at Molenbeek, 1642."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

to jump over the bridge leading up to the shrine, the sufferer would be free of illness for one year. However, by the time of Hondius's engraving, the hystericoepileptic systems of the female supplicants were occasionally construed as a sign of a mass outbreak of either dancing mania or demonic possession, which is why Hondius portrays the afflicted women being forcibly thrown off the bridge and into the river below—cold water being the only known cure for such conditions [5, 30, 49–52].

The symptoms of these pilgrim women were said to have been swelling of the abdomen, "pain and dejection, uncontrolled screaming, swooning, convulsive movements … after which the victims fell senseless to the ground." As such, it was not much of a conceptual stretch for even casual observers to interpret these symptoms as related to suffocation/strangulation of the womb [5, 49]. We should not be surprised that it was Paracelsus—the man who burned Avicenna's books in a public bonfire and declared nature to be "the sole origin of diseases"—who raced to the rescue of science by vehemently rejecting the notion that demonic possession caused this or any other illness. Instead, Paracelsus hypothesized that hysterical convulsions could stem from three possible sources: (1) "imagination," (2) "sensual desire," or (3) "corporeal causes" [49].

Of the corporeal causes, Paracelsus insisted that the uterus's "own elements" could "[turn] on itself," thereby causing uterine contractions [29]. Even though the

evidence was scant, these accounts of hysteric-epileptic-maniac pilgrims would find their way into the history of women's medicine by way of Syndenham and Charcot, two nineteenth-century authorities on "hysteria," who would later cite these stories as proof that the phenomenon of mass hysteria was possible, which in turn supported their hypothesis that hysteria was a psychological condition [49].

Illness as witchcraft Situated in this peculiar new, culturally specific framework, we can see how vestiges of the original *hysterikos* concept were both transmitted and transformed through time, the subject of endless reinterpretation depending on prevailing cultural influences. Although the concept of demonically induced illness was deeply influenced by folkloric notions of illness, nevertheless popular beliefs do provide important insight into how societies as a whole may have viewed women who suffered from symptoms of pain. Considering that these events at St. Vitus's shrine occurred during an era when an estimated 20,000 to 40,000 people were burned alive at the stake for supposedly engaging in witchcraft, then it becomes clear that societal perceptions of illness could even have fatal consequences (Fig. 2.21).

Fig. 2.21 Painting from seventeenth century depicting the devastating consequences of a plague outbreak in Naples, Italy. Allusions to supernatural forces as a causative factor are symbolized by the witches that can be seen flying in the air on brooms. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by D Gargiulio titled "Die Pest in Neapel 1656" [Plague scene in city], Call No. WA 100 C25, No. 4, box 12 sub.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Nothing exemplifies these shifting narratives of illness better than the unsettling accounts found in the court records of women being convicted for and sometimes tortured and executed as a consequence of their hysterical conditions, a fate permissible under the statutes from England's Witchcraft Act of 1604 [53–56]. To trace this unfortunate departure from scientific medicine, the commentary provided by physicians of the era becomes key to understanding the controversies under consideration. At issue was whether hysteria was an organic uterine pathology, a form of mental illness, or the consequence of supernatural events.

The transcripts of a seventeenth-century witchcraft trial in which Dutch physician Johannes Weyer (also Weir) (1515–1588) was called in as an expert witness to provide unique insight into these debates. Effecting tones of overt indignation, Weyer did his best to persuade the court that hysteria was unquestionably an organic condition, a "bodily disease like all other medical conditions" [7]. Had there been doubt about whether persecutions figured into the history of women's medicine, Weyer's next statement shatters any lingering incertitude. Imploring the courts to end their practice of "torturing and killing women," Weyer exclaimed, "Don't you know that these poor women have suffered enough? Can you think of a misery anywhere in the world that is worse than theirs? If they do seem to merit punishment, I assure you, their illness alone is enough" [29].

In another witchcraft trial of 1602, English physician Edward Jorden explicitly mentioned hysteria's connection to menstruation when he was summoned to court as an expert witness. In this case, the woman on trial was not the one suffering from hysteria. Rather she was accused of using witchcraft to cause the disorder in her neighbor's teenage daughter. Defending the accused woman vigorously, Jorden asserted that all of the teenage girl's presumed symptoms of possession actually pointed to hysteria, a condition he viewed as a uterine pathology triggered by menstrual irregularities [7]. As for the erratic nature of the symptoms, the "tics, swoonings, [and] convulsions," Jorden described these as simply signs of illness, which should not be "imputed to the Divell" but rather to "true naturall causes" [7].

Few, if any, had advanced a plausible theory to explain the choking fits considered for centuries to be a common symptom of suffocation of the womb. Yet here again Jorden was at the forefront, countering claims of demonic possession by explaining that "another argument of theirs is the offence in eating, or drinking, as if the Divell ment to choake them therewith. But this Symptom is also ordinarie in uterin affects" [57]. Despite Jorden's efforts, the defendant, Elizabeth Jackson, was sent "to the pillory" for punishment [29] (Fig. 2.22). Jorden was so disturbed by this outcome that he published the monograph, A *Briefe Discourse of a Disease Called the Suffocation of the Mother*, with the hope that its edifying message would help spare other women the fate that Elizabeth Jackson endured. Historian William Coventry provided an insightful analysis of these unfortunate moments in history when he observed that: "the spectacle of young girls screaming, crying, choking, and convulsing in court as they accused innocent people of sending murderous specters to harm them created an enormously compelling scene" [53].

Fig. 2.22 A painting from 1892 depicting a woman convicted of witchcraft who has been sent to the pillory for punishment. (Reproduced courtesy of the U.S. Library of Congress. Painting by Geo H. Walker, titled "The Witch, No. 2" [1892].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Nymphomania and Lovesickness

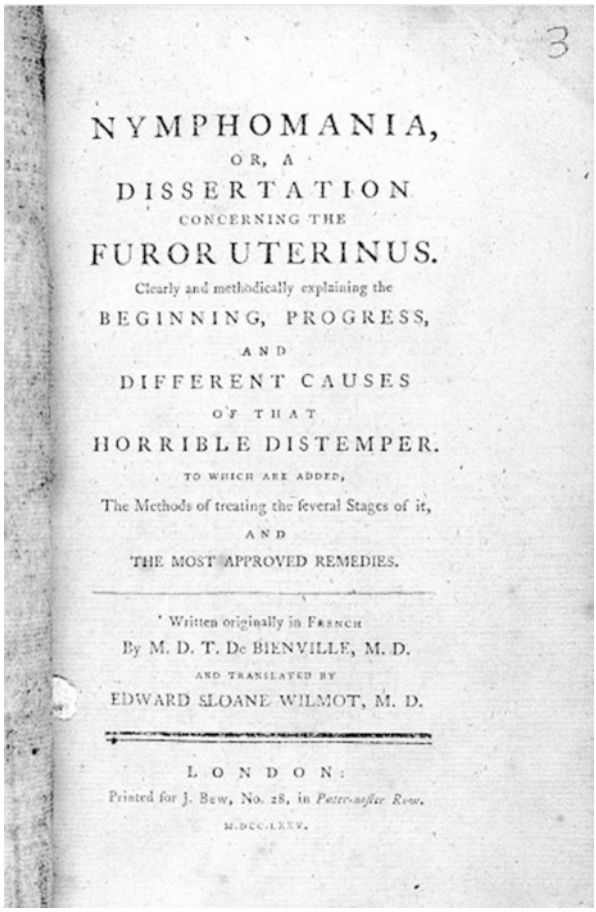
Although demonology would eventually be discredited by the eighteenth century, the physical-psychological etiologic divide, couched at times in accusatory undertones, would linger in the background of women's medicine well into the twentieth century. During this era of etiologic chaos, hysteria was sometimes diagnosed as nymphomania, also referred to as madness from the womb, womb-fury, and furor uterinus. Regardless of the name, all were undeniably suggestive of willful moral depravity, an "immoderate inclination to venery" as one seventeenth-century physician put it [58]. Outbreaks were said to have even occurred in convents. Diagnosing the purportedly afflicted nuns with "hysteromania or … erotomania," French physician Claude Quillet exclaimed, "These poor little devils of nuns, seeing themselves shut up within four walls, become madly in love, fall into a melancholic delirium, worked upon by the desires of the flesh, and in truth, what they need to be perfectly cured is a remedy of the flesh." In the most "extreme cases" of nymphomania, some even recommended that afflicted women be strapped into straitjackets [59–61].

Two of history's most prominent female figures, Marie Antoinette and Pauline Bonaparte, would become ensnared by this milieu of morally mediated disease constructs, as both were eventually accused of nymphomania. In the case of Marie Antoinette, the gynecologic disorders that she suffered from most of her adult life were no doubt counted as evidence against her. Pauline Bonaparte, on the other hand, was given the diagnosis of nymphomania specifically after visiting her doctor for pelvic pain [62, 63] (Figs. 2.23 and 2.24).

Fig. 2.23 Having suffered from gynecologic disorders most of her life, Marie Antoinette was among countless women through the ages whose conditions were sometimes perceived to be signs of nymphomania. (Reproduced with permission of the Wellcome Library, London. Engraving by Jean Duplessi-Bertaux, image no. L0010596.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Lovesickness, a decidedly more innocent version of nymphomania, also emerged as a folkloric explanation for women's illness. It was rooted in concepts of not only *hysterikos* but also a type of melancholy madness that had been proposed by Galen and other ancient authorities [30, 64]. Just as in ancient times, young women were viewed as especially susceptible to such disorders, as dozens of seventeenth-century paintings devoted to both nymphomania and lovesickness suggest [5, 7, 48, 64]. Yet, it was not just popular culture that had been influenced; in university archives across Europe, hundreds of medical dissertations list furor uterinus or nymphomania as the thesis topic (Figs. 2.25 and 2.26).

Backward steps in women's medicine These new concepts of illness represented several backward steps in women's medicine. First, disorders viewed as gynecologic for thousands of years were now being defined as *psychological in nature*. Far from being an innocuous shift, this change would end up negatively impacting women with endometriosis well into the twentieth century. And these were not just theoretical musings—nymphomania was still listed as a disorder in the International Classification of Disease until 1992 [58].



NYMPHOMANIA,
OR, A
DISSERTATION
CONCERNING THE
FUROR UTERINUS.
Clearly and methodically explaining the
BEGINNING, PROGRESS,
AND
DIFFERENT CAUSES
OF THAT
HORRIBLE DISTEMPER.
TO WHICH ARE ADDED,
The Methods of treating the several Stages of it,
AND
THE MOST APPROVED REMEDIES.
Written originally in FRENCH
By M. D. T. De BIENVILLE, M. D.
AND TRANSLATED BY
EDWARD SLOANE WILMOT, M. D.
LONDON:
Printed for J. Bew, No. 28, in Paternoster Row.
M.DCC.LXXV.

Fig. 2.24 An eighteenth-century treatise by French physician T. D. de Bienville was highly influential in introducing the concept of nymphomania into the popular conscience. (Reproduced with permission of the Wellcome Library, London. Image no. L0026663; Title page of T. D. de Bienville's *Nymphomania, or, a dissertation concerning the furor uterinus, clearly and methodically explaining the beginning, progress, and different causes of that horrible distemper,* English translation published in 1775.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Because certain illnesses were now perceived to be indicators of immorality, women were sometimes also blamed for their own illnesses [7]. In this case, not only were images of mad, lascivious wombs influencing popular notions about women and illness, but now the derisive concept known as the "curse of eve" had also seized the popular imagination. Derived from a misinterpretation of the Biblical passage Genesis 3:16, the curse of eve concept originally suggested that women were cursed by God to endure painful childbirth labor, but it was later distorted even further to include painful menstruation [65–67].

Ridicule in literature These sensationalized motifs of illness were especially popular sources of satire, and many were incorporated into popular literary works, including those of Shakespeare, in which female characters faked or otherwise wielded their hysterical condition to attract attention, manipulate men, or escape from domestic responsibilities [7, 29]. For example, in the novel *The Life of Gargantua and of Pantagruel*, the 1534 satire by physician-author Rabelais, women with hysteria are clearly targets of satire.

Fig. 2.25 A seventeenth-century painting in which a young woman is shown being examined by a physician. The imagery alludes to the concept of lovesickness, with the orange, a symbol of fertility at the time, being held to the woman's pelvic area as just one image indicative of these ideas. (Reproduced with permission of the Wellcome Library, London. Image no. L0017889; oil painting after Richard Brakenburg [1650–1702], titled "A medical practitioner taking a girl's pulse and holding a flask of her urine, with four other figures on the left and a maid opening a door on the right."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.26 A satirical painting from 1663 in which a young woman presumed to be suffering from lovesickness is depicted being treated by a doctor. Scholars who have studied this painting suggest that the artist used the term lovesickness to euphemistically allude to the concept of a wandering womb, for which sexual activity was considered the only known cure. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Jan Steen, titled "The Doctor's Visit" [ca. 1663].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Nevertheless, some of their portrayals actually offered some of the most insightful views to date about the physical symptoms of hysteria, with one character explaining that: "the movements [of the womb] sometimes [are] so violent that the woman is thereby deprived of all other senses and power of motion, as though she had suffered heart-failure, syncope, epilepsy, apoplexy, or something very like death" [29]. Even though the uterus is clearly implicated as the source of the symptoms, those suffering from the condition are still viewed as socially and sexually deviant, as expressed by another character from the Rabalais novel, who explains that: "those virtuous women who have lived modestly and blamelessly, and who have had the courage to rein in that unbridled animal and to make it obedient to reason, are deserving of no small praise indeed … once this same animal is glutted, if glutted it can be … then all these specialized motions come to an end, all appetite is satiated, and all fury appeased" [29].

The Physical-Psychological Divide

Historical vignettes like these appear to evince an absence of scientific thought, but the story is far more complex. While the seventeenth century marked the time during which Galileo was on trial and the humoral framework of disease predominated, it was also an era in which some of history's most revolutionary discoveries were made and was the same era in which [30] Bacon, Locke, Newton, Halley, Voltaire, and Rousseau all hailed [30] (Fig. 2.27).

A similar duality continued to characterize the debates about hysteria, which remained divided along the physical-psychological etiologic fault line. However, biases in historical reporting have no doubt skewed our understanding of these academic disputes. For example, with countless caricatures of wild, hysterical women looming large in the popular imagination of the period, those fantastical images are bound to capture the attention of medical historians, who frequently then privilege these sensationalized accounts over the comparatively dry clinical realities portrayed in conventional medical texts. This tendency to prefer more exotic explanations of illness is exemplified by the sentiments of Peter Mitchell, a historian of seventeenth-century medicine, who expressed dismay that the theory of hysteria as a psychological disease "fell on the deaf ears of a medical profession seemingly steeped in the utero-centric model of female physiology and pathology" [68].

Violent menstruation as a trigger in hysteria When we factor into our analysis the biases of historical reporting, it becomes clear that scientific medicine was not only thriving but had catalyzed an awakening interest in matching clinical results more carefully with the pathologic findings obtained by autopsy. In fact, the emerging discipline of pathologic anatomy ultimately helped rescue hysteria from falling further into etiologic wastelands. Even though some fringe groups still attempted to categorize hysteria as a pyschological-neurologic disorder, the uterine-menstrual connection held strong as one of the most credible theories of pathogenesis. As a

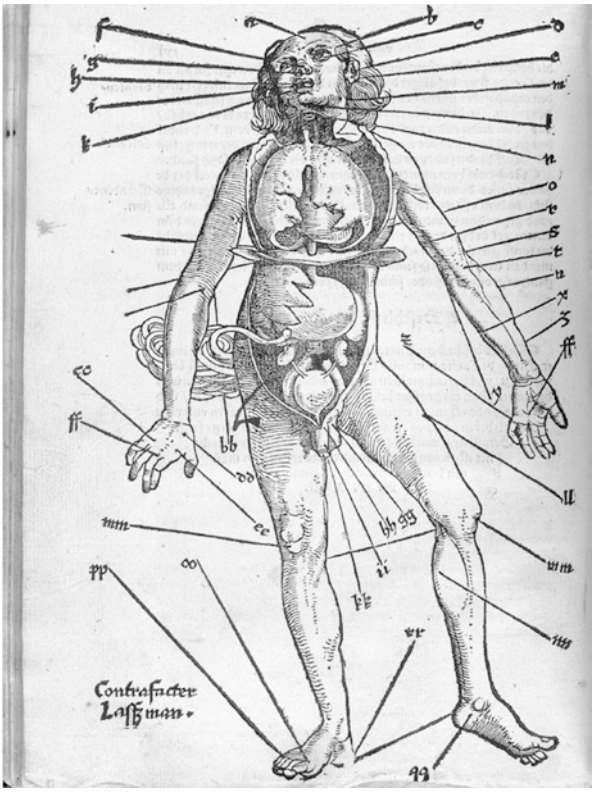


Fig. 2.27 A sixteenth-century surgical textbook etching illustrating the best areas of the body in which to perform bloodletting. (Reproduced courtesy of the U.S. National Library of Medicine. Medical textbook published by Hans von Gersdorff [circa 1455–1529] from *Field Book of Surgery* [Strassburg 1519].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

result, many physicians were acknowledging that hysteria was primarily the result of menarche "rampaging furiously throughout the body, causing violent paroxisms and anatomic upheaval," which "wreaked vast physiological damage" [7].

A synthesis of views With our subject so inextricably linked to blood, it should come as no surprise that the great blood doctor himself, William Harvey, offered his own take on hysteria.

Remarkably, Harvey's belief that sexual abstinence or unhealthy menstrual blood (aka, spoiled menstrual blood) could cause hysteria was nearly identical to theories that had been postulated by the Hippocratic authors 2000 years earlier. Explaining his views, Harvey observed "how many incurable diseases of the blood are brought about by unhealthy menstrual discharges … or from over-abstinence of sexual intercourse when the passions are strong" [5, 29]. Harvey warned that if women "continue too long unwedded" they will be "seized with serious symptoms—hysterics, furor uterinus, or fall into a cachectic state, and distempers of various kinds" [7].

It seems clear that Harvey believed both the menstrual/uterine and hungry womb theories simultaneously, but ultimately science prevailed, and Harvey eventually favored an organic explanation. In fact, Harvey was one of the earliest in modern

times to observe a connection between ulcers of the uterus and hysteria. While treating one of his patients for an ulcer of the uterus, he noted that, when he dilated the uterus, it contracted and made the woman suffer the same symptoms as those of hysteria. Harvey relied on this experience as definitive proof that hysteria was a uterine condition after all [29]. Harvey's remarks also demonstrate that reputable physicians from recent history had noted hysteria's unequivocal connection with menstruation [7].

Menstrual disorders and refluxed blood Some of Harvey's contemporaries also made it clear that they were not completely sold on the psychological nature of hysteria. Rather, seventeenth-century practitioners continued to challenge this notion by repeatedly emphasizing the organic and menstrual connection. Like Harvey, English physician Thomas Willis (1622–1675), recognized today as the founder of neuroscience, presented a mixed picture of hysteria that sometimes referred to its perceived organic aspects while leaving room for the possibility of psychological elements. For example, Willis suggested that hysteria "most often happened to the Female Sex, in whom the menstrual flux and other accidents of the womb, do challenge a part in the morbific cause." Yet he began to depart from this view after performing autopsies on women diagnosed with hysteria, whose uteri appeared to be normal. This apparent absence of pathology helped convince Willis that other psychological-neurologic elements must be involved [29]. Having the acclaimed nerve doctor himself allude to a neurologic etiology was enough to set off a whole new wave of speculation about hysteria's true nature. In the aftermath, the utero-centric edifice could be seen crumbling anew, leaving the door wide open for behavioral and psychological etiologies to continue festering in scientific medicine (Fig. 2.28).

Contrast these views to the work of renowned German anatomist Johannes Vesling, whose publication from 1647 introduced the idea that "extravasation of blood into the genital track" could cause uterine tumors [69]. Vesling's original work is not available, but if we accept as accurate the nineteenth-century second-hand account of his work, Vesling's observations would be the earliest instance in modern times that a refluxed-blood theory had been introduced to explain the presence of pathologic uterine growths.

Thomas Sydenham

A disease of civilization Despite the preponderance of evidence pointing to an organic condition specifically located in the uterus and associated with the onset of menstruation, hysteria was increasingly classified as a psychological-neurologic disorder. This convincing alternative was made all the more plausible when autopsies continued to reveal no identifiable pathology.

Of all the seventeenth-century practitioners to postulate an alternative to the uterine etiology, Oxford-educated physician Thomas Sydenham (1624–1689), known

Fig. 2.28 While others were beginning to view hysteria as a neurologic-psychological condition, English anatomist Thomas Willis (1622–75) generally believed it had an organic etiology, suggesting that it would "most often happen to the Female Sex, in whom the menstrual flux and other accidents of the womb, do challenge a part in the morbific cause." (Reproduced courtesy of the U.S. National Library of Medicine. Cover of Thomas Willis's *Pathologiae Cerebri et Nervosi Generis Specimen* [1667], Call no. 7128.5.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

as the English Hippocrates, provided the most impetus to the growing popularity of the psychological-neurologic theory of origin (Fig. 2.29). This was surprising, because Sydenham embodied some of the best attributes of the new scientific era. He believed, for example, that experiments were useless unless they could be duplicated by others. It was even reported that Sydenham's legendary disdain for untested book learning was so excessive that, when a student asked which medical books should be studied, Sydenham replied "Read Don Quixote" [30]. The story may be apocryphal, but it reflects the Enlightenment spirit of rigorous scientific investigation.

A disease of frayed nerves Enlightened or not, the precedent had been set by Willis and others for categorizing hysteria as a psychological-neurologic affliction. Perhaps it was because the mind represented the ultimate unknown in medicine that Sydenham found himself enthusiastically subscribing to the notion of hysteria as an exotic new disease construct, perhaps a "disease of civilization," the consequence of "frayed nerves as a result of the growing industrial age" [7]. In fact, Sydenham felt that hysteria was not only increasing in lockstep with the advancing industrial age, but that it was reaching epidemic proportions. And, as many others had suggested

Fig. 2.29 Although English physician Thomas Sydenham noted many symptoms of hysteria with striking correlations to endometriosis, such as hysterical lumps, hysteria of the stomach, vomiting, diarrhea, and back pain, he still concluded that its etiology was psychological in nature, perhaps the consequence of "frayed nerves as a result of the growing industrial age." (Reproduced with permission of the © National Portrait Gallery, London. Portrait by Mary Beale [1688].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

over the centuries, he also believed that it was particularly rampant among upper-class "leisured ladies" whose lives were often characterized by idleness and overindulgence, behavioral influences thought to be predisposing factors to hysteria [7].

"Cyclical" symptoms However, despite his preconceptions, Sydenham described a diagnostic profile that bore a remarkable resemblance to our modern understanding of endometriosis. His recommended treatment was a "hysterical pill" containing predominantly opium for the cyclic and erratic pains. Moreover, he was aware that "cases where pain in the bladder and retention of urine occurred" were commonly misdiagnosed as calculus [7, 40].

Hysteria of the stomach In connection with what was called "hysteria of the stomach," Sydenham noted that continuous vomiting and diarrhea were common symptoms [29]. Reports of mysterious lumps also returned to the diagnostic profile, with Sydenham reporting that "hysterical lumps" occurred throughout the body [40]. Sydenham also viewed the back pain reported by hysterical women as the disorder's most reliable diagnostic feature [29].

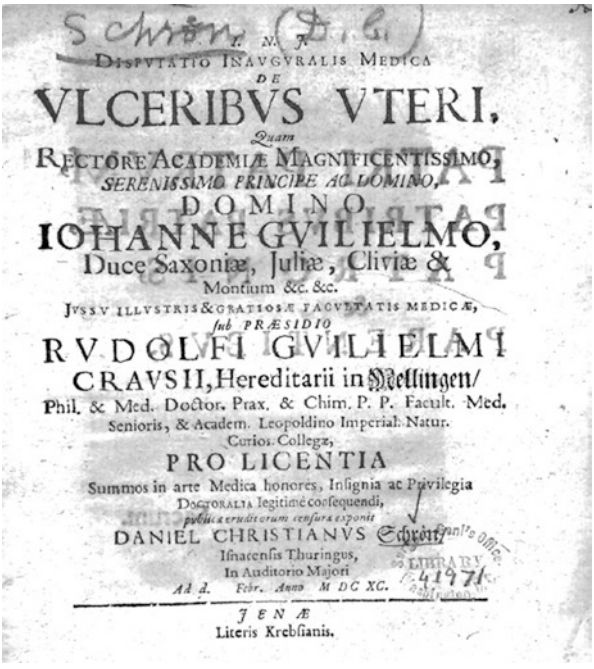
Far from being contemptuous of women with hysteria, Sydenham repeatedly demonstrated his profound empathy for those suffering from the disorder. His view was that the pain suffered by hysterical patients was more severe than that of other diseases, adding that, aside from fevers, "of all chronic diseases … hysteria is commonist" [7, 29].

Daniel Schrön

With their illness now situated within the context of psychological disorders, women experiencing unidentifiable ailments were left especially vulnerable to misdiagnoses. Still, by the late seventeenth century, an era characterized by a growing interest in morbid pathology, a few physicians held a completely different point of view. They departed from the hysterical disease construct in favor of focusing nearly exclusively on the physical signs of uterine pathology.

One such investigator was the German physician Daniel Schrön, identified by Vincent Knapp as one possible early pioneer. In Schrön's 1690 dissertation on ulcers of the uterus, several gynecologic symptoms were described that bear some similarity to those of endometriosis [30, 70] (Fig. 2.30). In view of the many outstanding ambiguities and controversies that have followed Knapp's interpretation of Schrön's work, we analyzed the original Latin language thesis ourselves and found credible evidence to support Knapp's conclusions. Though a certain margin of error is assumed in translating a 322-year-old medical document from Latin, we can confirm with a reasonable level of confidence that Schrön indeed may have been describing endometriosis in many cases.

Fibrous, glandular, and spongy membranous parts of the uterus Schrön begins his thesis by delineating the multiple types of tissue that could be found in the uterus, such as fibrous, glandular, and "membranous" parts. In an age when few used the still-primitive microscope technologies available, Schrön's ability to report


S. Schrön. N. 7.

DISPVTATIO INAVGVRALIS MEDICA

DE

VLCERIBVS VTERI,

Quam

RECTORE ACADEMIÆ MAGNIFICENTISSIMO,

SERENISSIMO PRINCIPE AC DOMINO,

DOMINO

IOHANNE GVILIELMO,

Duce Saxoniæ, Juliæ, Cliviæ &

Montium &c. &c.

JVSSV ILLVSTRIS & GRATIOSÆ FACVLTATIS MEDICÆ,

sub PRÆSIDIO

RVDOLFI GVILIELMI

CRAVSII, Hereditarii in Mellingen/

Phil. & Med. Doctor. Prax. & Chim. P. P. Facult. Med.

Senioris, & Academ. Leopoldino Imperial. Natur.

Curios. Collegæ,

PRO LICENTIA

Summos in arte Medica honores, Insignia ac Privilegia

DOCTORALIA legitimè consequendi,

publicæ eruditorum censuræ exponit

DANIEL CHRISTIANVS Schrön/

Ilmacensis Thuringus,

In Auditorio Majori

Ad d. Febr. Anno M DC XC.

JENÆ

Literis Krebsianis.

Fig. 2.30 Title page of seventeenth-century physician Daniel Schrön's dissertation, which contains descriptions of clinical and macroscopic signs and symptoms highly suggestive of endometriosis. *Nezhat. Endometriosis in history. Fertil Steril 2012*

distinctions of such accuracy demonstrates a sophisticated anatomic knowledge that many medical historians assume had yet to be secured by that period. And, by paying homage to the many renowned anatomists of his era, such as Bartholin and de Graaf, Schrön establishes that even early sixteenth-century anatomists had a much more sophisticated understanding of different tissue types than has been commonly assumed in modern times.

To demonstrate this sophisticated knowledge, Schrön explains that "Bartholinus, that celebrated anatomist, considers that the membranous part in the substance of the uterus is the product of two sources, and … that one of these … is from the peritoneum, whilst the other is unique … which however one cannot differentiate, except in the case of ulcerated abscesses. We have seen that enclosed within these internal and external walls, there is a fleshy layer composed of flesh-like fibres, resembling those internal organs … [and] a spongy layer full of hollows, containing countless little tubes." Descriptions as remarkably accurate as these may seem unbelievable; however, even though the microscope was in its infancy at the time, anatomists of the era were able to observe such intricacies with the help of fairly powerful magnifying glasses [71].

Swelling "globules" Schrön goes on to provide another description that is remarkably similar to modern observations, stating that "the anatomists also describe a glandulous layer or, if you prefer, a layer full of little gland-like corpuscles" [70]. It is these tissue elements, Schrön says, that can undergo ulceration and change shape; he explained that "when their action is disturbed, they become the agents of many kinds of fermentation … and develop into a new substance which is hard and much bigger, like the glandulous bodies, or if you prefer, little balls [globules] not dissimilar to the hardened yoke of an egg that Regner de Graef observed in his 'Treatise on the Organs of Women' … from which the formation of a hard swelling develops" [70].

Deep ulcers "under the surface" As for the many types of ulcers observed, Schrön notes that, though "the eyesight of the surgeon cannot penetrate all ulcers," there are types that reside "deep under the surface" of the uterus [70]. Remarkably, Schrön noticed that such ulcers appeared to have developed at different times, an observation with uncanny parallels to modern understandings of how older lesions can be distinguished from newly established ones. Expanding on these findings in more detail, Schrön states, "Some furthermore are recent, others well-established, others again dirty, of evil character, cavernous or filled with tubes, cancerous, etc." [70].

Nonsyphilitic lesions While his descriptions could suggest many different types of ulcers, Schrön is careful to differentiate these lesions from other common conditions of his era, such as "sores, abscesses, small pox, scabies, etc." as well as pathologies he describes as "sexual" diseases, with syphilis mentioned specifically [70]. As for those most susceptible to the disorder, Schrön observed, "It is when women are of a timely age to marry that they are particularly assailed by these ulcers" [70].

Descriptions of symptoms Concerning the pain, he notes, "Once again, among the essentially inherent signs of uterine ulcers it is pain which forms the preeminent feature; when this is at its most intense, as Plater testifies in the cited work, then, from the pain, or tearing and stinging sensation which acts in various ways, uterine ulcers are named as the problem" [70].

Preliminary refluxed blood theory Schrön also suggests that bleeding (presumably menstrual, though this is not explicitly stated) may occur in other parts of the pelvic area besides the uterus. To address this potentiality, Schrön suggests that other areas of the pelvis outside of the uterus should be examined for signs of this ulceric condition, such as painful tenderness. He explains that these ulcers can arise outside of the uterus due to what he describes as the known ability of uterine blood to travel outside the uterus, causing the lesions. Explaining this observation in detail, Schrön reports:

> For a flow of blood can also arise outside the sphere of the uterus, and for this reason, as it often deceives the doctor, the sense of touch must be invoked for assistance. If ulcers have a fixed location around the internal orifice or the exterior areas, then they can be investigated by touch on account of the extremely delicate sensitivity of the parts in the same area [70].

As for the collateral damage that uterine ulcers can cause, Schrön simply says, "The two possible outcomes are death or sterility" [70].

Stagnated blood origin To further explain why "stagnation" of menstrual blood would give rise to lesions, Schoen brings us back to the same ancient idea of spoiled menstrual blood that had been propounded for centuries by that time. Schrön offers a variation of this theory:

> There are various consequences of stagnation, including primarily inflammation. In addition all inflammation that is properly so-called afflicts the part with redness, heat, pain, and swelling, and, as the last and well-known characteristic, the power to suppurate. Having taken these facts as true, then tumors, abscesses, swellings, ulcers, etc. are readily allowed [70].

As for treatment options, in another uncannily modern view, Schrön concludes that "the principal remedy comes from surgery."

Hereditary disposition Concerning contributing factors, excessive menstrual bleeding is mentioned as a potentially predisposing factor [70]. As to other proximate causes, it is interesting to note that Schrön is one of the few we have uncovered to offer heredity as one possibility among many. Although a few allusions to this theory were made by the ancient practitioners we have covered, Schrön provides the most explicit declaration on the subject: "Nor clearly should one reject an hereditary disposition, because Sennert, in his work *Surgery* (book 5, chapter 17, page 11) notes that there are certain families in whom ulcers erupt as though it were by hereditary right, and others also have observed the same phenomenon" [70].

Ambiguous aspects As critics of Knapp's research have pointed out, other characteristics mentioned by Schrön have limited correspondence with endometriosis, such as descriptions of suppuration and pus. However, during that period, nearly every ailment was thought to stem from an inflammatory process, making it possible that Schrön's observations of pus and other signs of suppuration were simply interpretations conforming to the established belief systems of the day. In other words, rather than being accurate representations of the facts, his analyses may have been reflecting culturally produced notions of disease states. In any case, even twentieth-century investigators have detected elements that could be said to have pus-like coloring. In 1908, for example, endometriosis pioneer Thomas Cullen reported observing adenomyomas with "many … cyst-like spaces contain[ing] fresh blood or yellowish blood pigment" [72].

Moreover, it is not clear how many autopsies Schrön performed or whether the conditions under which cadavers were kept contributed to the degradation of tissues. Given these many extenuating factors, the entirety of Schrön's work should not be indicted merely for an observation of pus, which may, in any case, have been a forgivable misinterpretation of the tissue specimens under inspection.

The other ambiguous aspects of Schrön's work relate to his statements concerning vaginal excretions. Before drawing any conclusions, it is helpful to consider the entire paragraph from which these statements about vaginal excretions were drawn:

> Most of all the complaint is made manifest by excretions of various colors, such as bright yellow, dull yellow, green, dark purple, black, muddy, and stinking, which flow from the uterus and stain linen [underwear] with various colors, either at intervals or continually, in accordance of course with the manner in which the matter is flowing. Fernel agrees with these, and states that an aggregation of corrupt blood drips out; it is varying in quantity, substance, and color, sometimes stinking, but at other times lacking any smell, while at times the sort of matter emerges that can only with difficulty be differentiated from a normal flow.

The descriptions of "dark purple, black, muddy" excretions, and "an aggregation of corrupt blood" could point to endometriosis, but the other descriptions prove too ambiguous to be of any help. Schrön also viewed this wildly disparate clinical picture as confusing. In fact, to address the dilemma of trying to differentiate between these various discharges, particularly that of normal menstruation as opposed to menstruation accompanied by ulcers, Schrön resorts to invoking the tenants of the ancient master, Galen, advising that "as a result, Galen, *De Locis Affectis,* chapter 5, states that unmistakable visible signs of a menstrual flow must often be sought."

These interpretations of Schrön's work may still be viewed as inconclusive and contested, but after considering the textual evidence in its totality, we do not feel that two areas of ambiguity—pus and confusion over the nature of vaginal discharge—are sufficient grounds for summarily discrediting the idea that endometriosis could have been the disorder Schrön was observing. Overall, enough passages have clear parallels to modern perspectives that it is entirely plausible that Schrön was indeed witnessing cases of endometriosis. Schrön provided remarkably accurate differential diagnoses, distinguishing the ulcers he observed from those

deriving from syphilis, for example. Additionally, the clinical signs he reported correlate to the same cluster of symptoms and physical manifestations that had been consistently observed for more than 2000 years. Among the most relevant of these were Schrön's descriptions of extreme pain, deeply embedded growths, swollen and painful globular-like nodules, old and new ulcers, and explicit associations with menstruation, particularly menorrhagia. By what appears to be a synthesis of centuries of observations—including those of Galen as well as his contemporaries such as Bartholinus, Regner de Graef, and Sennert—Schrön also achieved several breakthroughs, including the introduction of a rudimental theory of retrograde menstruation and recognition that the disorder was potentially heritable.

Frederik Ruysch

Another seventeenth-century investigator, the well-regarded Dutch anatomist Frederik Ruysch (1638–1731), also may have stumbled upon cases of endometriosis. Unlike Schrön, Ruysch was not identified by Knapp, but instead was repeatedly cited by several early to mid-nineteenth-century physicians who had discovered for themselves a disorder that was most likely endometriosis (Figs. 2.31, 2.32, 2.33 and 2.34). Like Schrön, Ruysch advanced his own version of a reflux theory, suggesting that congenital malformations of the uterus obstructed menstrual blood, which caused the blood to back up and spill into the peritoneum, thereby causing pain,

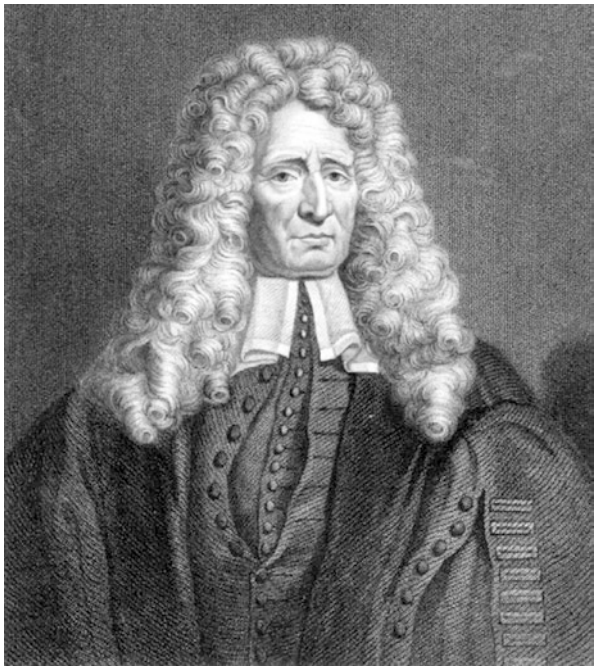


Fig. 2.31 Portrait of Frederik Ruysch (1638–1731), acclaimed seventeenth-century Dutch physician and anatomist, whose works include descriptions of refluxed blood in the peritoneum and other clinical symptoms somewhat suggestive of endometriosis. (Reproduced courtesy of the U.S. National Library of Medicine. Engraving published by J. Wandelaar and J. Jenkins; Call no. 5890.3.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.32 A painting from 1683 in which Ruysch is depicted performing an autopsy for his students. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Jan van Neck [1683], titled "The Anatomy Lesson of Professor Ruysch."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

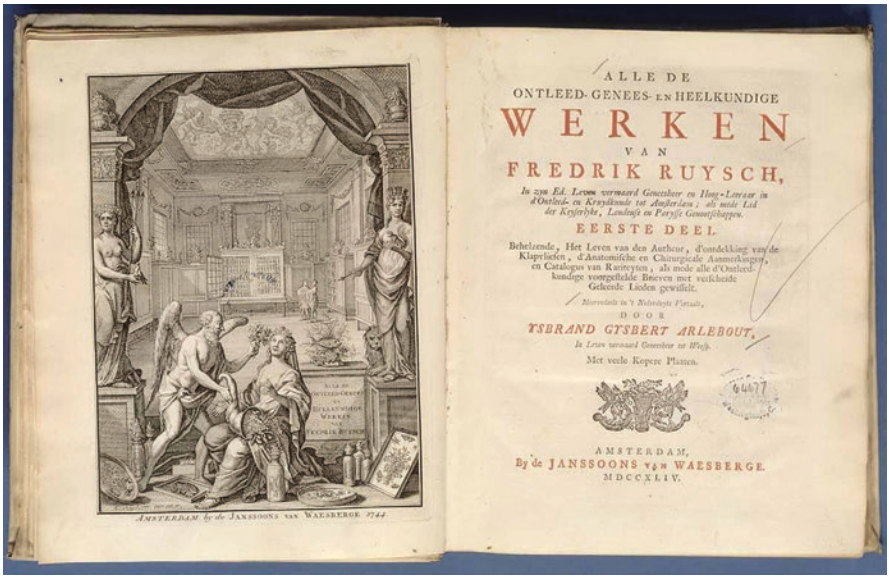


Fig. 2.33 Image of Ruysch's seventeenth-century textbook, title page, and frontispiece. (Reproduced courtesy of the U.S. National Library of Medicine.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

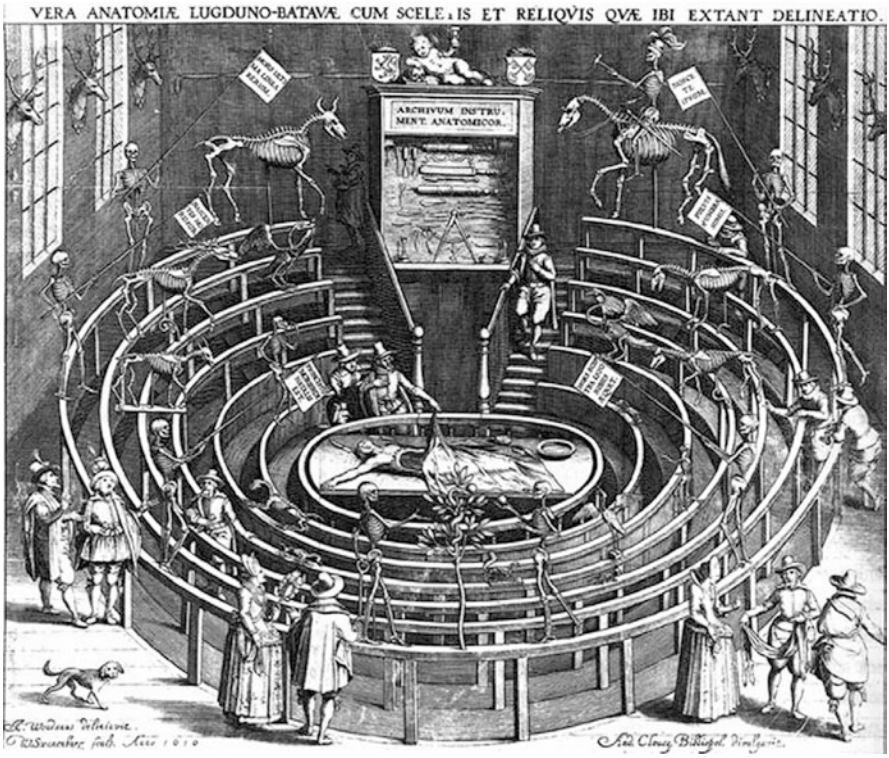


Fig. 2.34 As portrayed in this etching from 1610, the University of Leiden where Frederick Ruysch taught was especially progressive in the anatomical sciences for which the performance of autopsies played a central role. (Reproduced with permission of the Trustees of the British Museum. Etching by Willem van Swanenburg [1610], titled "Views of the University of Leiden; Plate 1."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

lesions, and inflammation [73]. However, Ruysch's theory departed from Schrön's in one crucial way: He believed the effusion of blood and subsequent formation of lesions occurred only when an obstruction to menstrual flow was present.

Ruysch reached his conclusions during an autopsy of a woman who had died of an unknown cause. During the postmortem analysis, Ruysch noticed two things that surprised him. First, he found that blood apparently deriving from the fallopian tubes had refluxed (referred to then as effused or extravased) into the peritoneum. The theory that this could occur had been circulated for years (recall Vesling's observation in 1647), but it was apparently still believed to be an anatomic impossibility, improbable enough that it was treated as an important discovery over a century later. Second, Ruysch noted that where the blood had spilled, lesions of some kind had developed. Running through the possible differential diagnoses, Ruysch apparently ruled out the possibility of an ectopic pregnancy. In the same medical textbook, but under a different section, Ruysch also relates his clinical findings from a young girl who had presented with pelvic pain and other symptoms

similar to those of the woman he had autopsied earlier. Upon examination, the girl was found to have a congenital obstruction to the flow of her menstrual blood [74, 75].

Based on his observations (and possibly on other works that have not been translated), Ruysch hypothesized that the refluxed blood found at autopsy and in the young woman with the congenital obstruction was the cause of the symptoms of pain and pathologic growths:

> In the anatomical observation of this corpse I also observed that the pelvis was full of the impure dregs of liquids, making very nearly two pints and a highly offensive smell, or possibly these liquids had been propelled from the uterus through tubes or egg-ducts into the pelvis, and I find this easy to believe because I have on a number of occasions discovered liquids in the pelvis resembling those which I found in the uterus [75, 76].

Regrettably, Ruysch's descriptions are exceedingly sparse, comprising only a few frustratingly obscure paragraphs. However, in one passage, Ruysch mentions clinical symptoms somewhat suggestive of endometriosis, which he says can now be explained by his autopsy results. Concerning these symptoms, he notes, "this is very often the source of those tears and complaints about an intolerable pain and chill in the area below the stomach, and blockages, and indeed not infrequently a continual flow of menstrual blood" [74]. From this condition, Ruysch explains, "there arise terrible fevers, agonies around the area below the stomach, loss of consciousness and similar ills, and death itself."

Schrön versus Ruysch Although Ruysch's work was later cited by others, Schrön, who preceded him by a year, should be considered the first in modern times to offer a brief but fairly clear reference to a reflux etiology. All the same, Ruysch's insights provide a crucial piece of evidence to support the notion that investigators were coming closer and closer to identifying what may have been endometriosis. In both Schrön's and Ruysch's works, the conceptual continuity with Sampson's theory of retrograde menstruation is remarkable. Given such similarities, it is all the more surprising that these ideas were apparently lost in history until Sampson resurrected them nearly two-and-a-half centuries later. Ruysch's underlying obstruction theory is also nearly identical to modern theories about Mayer-Rokitansky-Küster-Hauser syndrome, which studies suggest increases the likelihood that endometriosis will develop.

The Eighteenth Century

The works of Schrön and Ruysch serve as much needed counterpoints to the tales of madness, witchcraft, and demonology invading the sanctity of science. In contrast, their work clearly demonstrates many principles of scientific medicine were informing their analyses, especially the burgeoning field of pathologic anatomy, a discipline that appears to have been established long before its commonly assumed official founding by Giovanni Morgagni in the eighteenth century.

Eighteenth-century medical literature also continued to be loaded with descriptions of hysterical symptoms exhibiting striking parallels to endometriosis. One recent study analyzing admissions for the hysteria ward of an eighteenth-century Edinburgh infirmary found that most of the women diagnosed with hysteria had "loss of appetite or other digestive problems, menstrual difficulties, and fainting spells," symptoms suggestive of many organic diagnoses [7]. Just as Schrön had suggested in the previous century, the concept that hysteria could be inherited also continued to be advanced. In attempting to distinguish epilepsy from hysteric fits, a physician in 1702 observed that "Vapours as well as other Diseases [were] transmitted to us from our Fathers and Mothers," while apoplexies presumably were not [77].

Diary entries from women also serve as especially revealing sources for helping us understand hysteria's pain symptoms in particular. One undated entry from the diary of Lady Mary Montagu (1721–1751) was particularly haunting, she wrote, "I have seen so much of hysterical complaints, tho' Heaven be praised I never felt them, I know it is an obstinate and very uneasy distemper, tho' never fatal unless when Quacks undertake to cure it. I have even observed that those who are troubled with it commonly live to old age. Lady Stair is one instance; I remember her screaming and crying when Miss Primrose, my selfe, and other girls were dancing 2 rooms distant" [78].

Neuroses, Nymphomania, and Ovaries

Even with such an endless parade of physical symptoms and expressions of pain, the trend toward viewing hysteria as a nervous condition—or worse—seemed to march on unabated. Accusations of immorality or duplicity also remained in the background as explanatory factors, while others began viewing hysterical women as mentally deranged [7]. In such cases, women with hysterical symptoms were in danger of being sent to madhouses, such as Bedlam, a place people would visit for entertainment to "view the lunatics for a penny" [7]. One of the era's most respected "nerve" doctors, English physician William Cullen, was particularly influential in keeping alive the notion that hysteria was a psychological-neurologic disorder (Figs. 2.35 and 2.36).

Cullen's stance is all the more surprising upon discovering that he had observed hysteria to be connected to "menstrual difficulties," when too much blood in the uterus caused a "turgescence of blood" which in turn overloaded the body's vascular systems, including those of the brain. Of note, Cullen was even one of the first in our historical review to mention that the ovaries were somehow involved in hysteria, explaining that they were particular painful in hysterical women [29]. Remarkably, Cullen was able to deftly explain away all of these undisputed gynecologic symptoms by reframing them as part of his neurologic theory of origin, asserting that the vascular overloads caused by menstruation were triggering systemwide neural dysregulation [29]. Worse still, Cullen went on to implicate behavioral or psychological factors as the true causes, blaming the condition on "young widowhood, and to

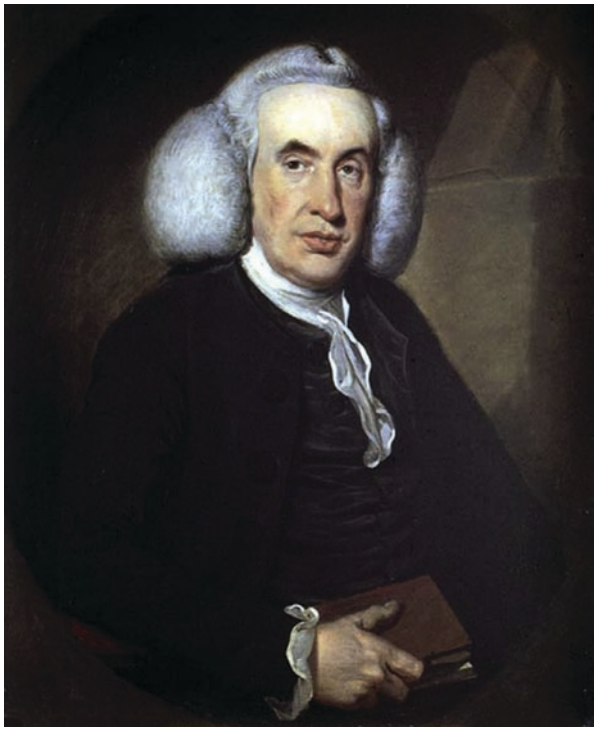


Fig. 2.35 Even though eighteenth-century English physician William Cullen noted hysteria's many physical symptoms, including its connection to "menstrual difficulties," he implicated both neurologic and behavioral factors, noting that "females liable to nymphomania" were especially prone to the disorder. (Reproduced courtesy of the Hunterian Library, University of Glasgow. Portrait by unknown artist.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

passions of a sensitive mind" and claiming that "females liable to nymphomania" were especially prone to the disorder.

As one can imagine, physicians themselves noticed that patients revolted against a diagnosis of hysteria. It was observed that women were thoroughly "unwilling to own a disease that [would] expose them to dishonour and reproach" [7]. Upon being diagnosed with hysteria, Queen Anne promptly fired her personal physician, indignant at the suggestion that she was mad, immoral, or imagining it all [7].

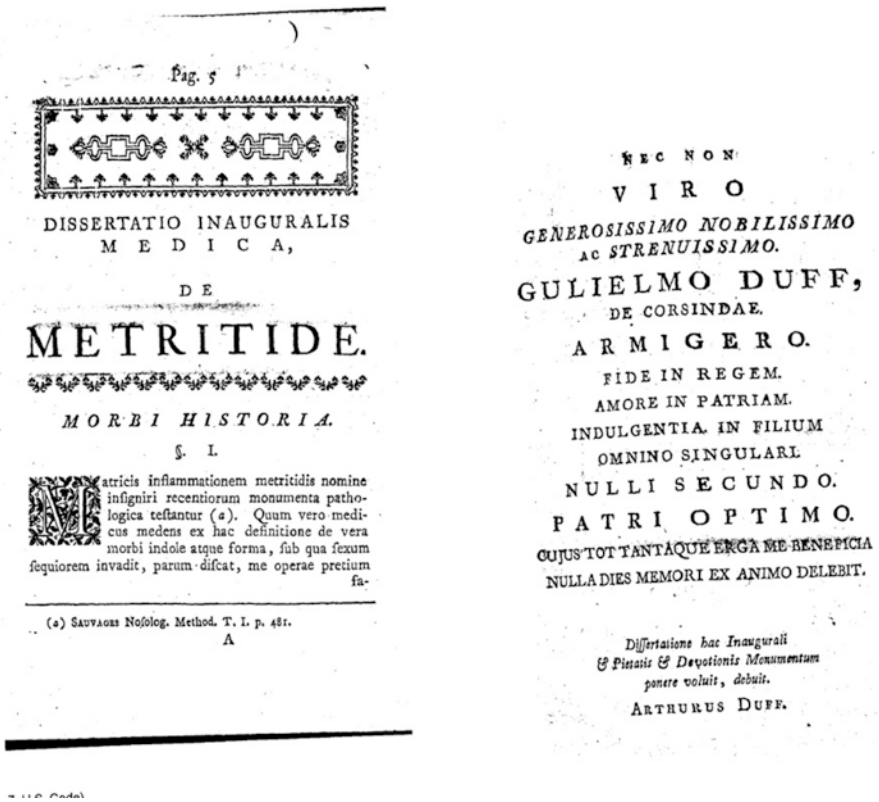
Arthur Duff

Although the voluminous chronicles of hysteria have attracted considerable attention from medical historians, in the background an endless stream of investigators had been studying the less dramatic but equally enigmatic disorder of inflammation of the uterus (endometritis or metritis), a condition that could also have been endometriosis in many cases. In fact, Arthur Duff, the Scottish physician identified by Knapp, dedicated his entire 1769 master's dissertation, "Dissertatio Inauguralis Medica de Metritide," to the subject of inflammation of the uterus (Fig. 2.37). With Duff's descriptions of metritis sufferers as experiencing intense and violent pain,

Fig. 2.36 Those with mental disorders, including women diagnosed with hysteria, were often imprisoned in mental institutes such as St. Bethlehem Hospital (colloquially known as Bedlam), where patients were physically restrained in prison cells with chains and strait jackets. (Reproduced with permission of the Wellcome Library, London. Engraving by Ambroise Tardieu from *Des maladies mentales,* by J.E.D. Esquirol; published by Bailliere, Paris, 1838 plate XXV.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

vomiting, uterine contractions, and bowel symptoms, an image of a disorder with remarkable similarities to endometriosis begins to emerge [79]. Duff began his dissertation by explaining that metritis had recently been the subject of great "fixation" by pathologists, but that physicians were falling considerably short of uncovering its causes and true nature [79].

Description of symptoms As for the terrible pain associated with inflammation of the uterus, just as the ancients had Duff describes women lying prostrate for days with nausea, vomiting, shivering, strangulation of the uterus, uterine contractions, convulsions, bowel and bladder symptoms, interrupted pulse, delirium, back pain, and "an unquiet mind." Duff notes that death is a possible outcome, explaining that "the patient is snatched away, though she deserves a better fate" [79]. Although Duff alludes to ulcers or lesions only briefly, he does mention that, upon the touch, the inflamed areas of the pelvic region are very painful for the patients [79].



Pag. 5

DISSERTATIO INAUGURALIS
MEDICA,

DE

METRITIDE.

MORBI HISTORIA.

§. I.

Matricis inflammationem metritidis nomine insigniri recentiorum monumenta pathologica testantur (a). Quum vero medicus medens ex hac definitione de vera morbi indole atque forma, sub qua sexum sequiorem invadit, parum discat, me operae pretium fa-

(a) Sauvages Nosolog. Method. T. I. p. 481.

A

NEC NON

VIRO

GENEROSISSIMO NOBILISSIMO
AC *STRENUISSIMO.*

GULIELMO DUFF,

DE CORSINDAE.

ARMIGERO.

FIDE IN REGEM.
AMORE IN PATRIAM.
INDULGENTIA IN FILIUM
OMNINO SINGULARI
NULLI SECUNDO.
PATRI OPTIMO.
CUJUS TOT TANTAQUE ERGA ME BENEFICIA
NULLA DIES MEMORI EX ANIMO DELEBIT.

Dissertatione hac Inaugurali
& Pietatis & Devotionis Monumentum
ponere voluit, debuit.
ARTHURUS DUFF.

Fig. 2.37 In Arthur Duff's seventeenth-century dissertation on metritis, he mentions several symptoms highly suggestive of endometriosis, including intense and violent pain that caused patients to lie prostrate for days with nausea, vomiting, strangulation of the uterus, uterine contractions, convulsions, back pain, and bowel and bladder symptoms. (Reproduced courtesy of the U.S. National Library of Medicine. Title page of Arthur Duff's dissertation titled *Dissertatio inauguralis medica de metritide* [1769]. Publisher Lugduni Batavorum, Apud Theodorum Haak, Call No. W4 L68 1769 D.1.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Menstruation and refluxed blood As for etiologic understandings, Duff reviews the prevailing theories of the era and eventually concurs that a menstrual disorder is at play, explaining that "it is clear that the proximate cause of metritis is provided by the vital movements of the arteries of the uterus, when they violently malfunction and are more forceful than natural movements, with the result that a significant quantity of blood is forced into this organ with an impetus that is greater than normal" [79].

Duff's circuitous manner of explaining things makes it difficult to discern his intended meaning. Based on other passages, it becomes clear that Duff is referring to the monthly engorgement of the uterus that occurs during menstruation. Adding to his hypothesis of a menstruation-related etiology, Duff further explains that "substances which have been forced back supply the irritant of a small amount of salt

which would normally pass through like sweat, as a result of which the quantity of matter that is driven back increases."

Although it has languished in historical obscurity, Duff's hypothesis that menstruation could trigger metritis was actually an unrecognized conceptual breakthrough. One reason Duff's insights should be considered exceptional is because our research indicates that throughout history endometriosis may have been mistaken for metritis in many cases. This hypothesis is plausible when one considers that nineteenth-century investigators expanded the disease profile of metritis to include chronic, hemorrhagic, and exfoliating metritis—variations with nearly identical symptoms as endometriosis and which are described as occurring with menstruation [30].

The Nineteenth Century

As exceptional as these eighteenth-century achievements were, studies on gynecologic disorders still seemed comparatively limited relative to other disciplines of medicine. As a result, for the next 200 years, our journey toward a long-sought, definitive understanding of endometriosis continued to be rife with uncomfortable uncertainty. But we have reached the nineteenth century, arguably one of the most spectacular centuries that medicine had ever witnessed, when some of the greatest milestones in women's surgery were achieved, including developments that would eventually prove beneficial for women with endometriosis.

One of the most triumphal moments of the new century occurred in 1809, when Ephraim McDowell of Kentucky performed the first successful abdominal oophorectomy, during which a 22-pound ovarian tumor was removed from Mrs. Jane Crawford, who, in that preanesthetic era, sang herself through the surgery and went on to live another 33 years (Fig. 2.38). A few years later, in 1815, the first planned vaginal hysterectomy on a patient who survived was performed by German surgeon Konrad Langenbeck. And by mid-century, improvements to the surgical sciences made it possible for Walter Burnham of Lowell, Massachusetts, to perform the first abdominal hysterectomy with a survivor in 1853.

However, as the surgical sciences began to flourish, a strange predicament arose. The growing need to supply medical students with corpses for autopsies gave rise to ghoulish tales of body snatching (Fig. 2.39). Equally strange relationships flourished. For example, the Barber-Surgery Company of London, the guild that regulated surgeons, actually sent Christmas gifts to executioners each year so that they would be guaranteed a steady supply of corpses. Poor families would be unduly burdened when in 1832 the Anatomy Act was passed in Britain, making it lawful to use the corpses of "unclaimed bodies," such as people who had died in factories or poor houses with no apparent family or those from families who could not afford burial expenses [30]. In France, cadavers were even more freely obtained; one medical student from 1835 noted in his diary that they were easily procured for just "half a franc" [30].

Fig. 2.38 American surgeon Ephraim McDowell performed the first successful abdominal oophorectomy in 1809, removing a 22-pound ovarian tumor from Mrs. Jane Crawford, who, in this preanesthetic era, sang herself hymns throughout the surgery and lived another 33 years. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Davenport titled *Ephraim McDowell* [*November 11, 1771–June 25, 1830*].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Fig. 2.39 Nineteenth-century satirical etching of bodysnatching in progress, which the artist has titled "A night watchman disturbs a body-snatcher who has dropped the stolen corpse he had been carrying in a hamper, while the anatomist, William Hunter (1718–1783), runs away." (Reproduced with permission from the Wellcome Library, London. Engraving by William Austin [1773], No. 25668i, L0001663 [also described as "The anatomist overtaken by the watch carrying off Miss W–ts in a hamper."). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Pioneering French Pathologists

The era's lively interest in the internal mysteries of corpses spearheaded the tremendous progress in the still-burgeoning field of morbid pathology, which would later play a decisive role in the eventual microscopic discovery of endometriosis. The discipline of morbid pathology was characterized by its emphasis on matching clinical observations to localized disease. In other words, the "symptoms had to correlate with any lesions or signs of disease in the tissue" obtained during autopsies [30]. By mid-century critical discoveries such as William Jenner's 1849 differentiation of typhus from typhoid were achieved as a direct result of postmortem investigations [30]. However, it was the French who were recognized as the leading pioneers in this new field of postmortem studies.

As one medical historian put it, "lesions were prized by Paris medicine as key to pathology" [30]. This new emphasis on conducting postmortem analyses was clearly evident in the works of Marie Francois Xavier Bichat, the French pathologist of tissue-specificity fame and the father of histology (Fig. 2.40). Exemplifying this new age of empirical medicine, Bichat proclaimed, "You may take notes for twenty years from morning to night at the bedside of the sick, and all will be to you only a confusion of symptoms … a train of in-coherent phenomena." Instead, Bichat proclaimed, the moment one starts to perform autopsies "this obscurity will soon disappear" [30].

Bichat and others still relied on magnifying glasses—with the exception of John Bennett, who discovered leukemia using a microscope [80]—but there was a greater

Fig. 2.40 Portrait of Marie François Xavier Bichat, renowned French anatomist, physiologist, and surgeon, known today as the father of modern histology and pathology. Bichat's contributions include advancing the notion that autopsies were essential to understanding diseases and that diseases attacked specific types of tissues rather than organs. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Godefroy Engelmann [1788–1839] after Pierre-Roch Vigneron [1789–1872].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

understanding that disease was actually specific to different tissues. That is, glandular and mucosal tissues rather than the organs themselves were considered important, and pathologic lesions were recognized to arise anywhere in the body that similar tissues were located. These revelations would one day play a key role in the eventual microscopic discovery of endometriosis [30].

Macroscopic discovery of endometriosis Given the clear lead of French pathologists in the postmortem sciences, it is not surprising that they were among the first in the nineteenth century to macroscopically distinguish what were in all likelihood cases of endometriosis. Their descriptions of a menstruation-triggered disorder were astonishingly identical to endometriosis, bearing all the characteristic clinical symptoms as well as macroscopic findings [30, 81]. As we have seen, countless references to dysmenorrhea and other menstruation-related disorders had been noted throughout the history of medicine, but what made the observations by this group of French investigators unique was that they finally were able to correlate clinical symptoms to the postmortem findings that revealed corresponding pathologies.

In this way, this group of French pioneers was finally able to sufficiently narrow the symptom profile, allowing for a distinct disease entity with distinct symptoms to finally emerge. Even though microscopic confirmations were not made at this time, the signs and symptoms were essentially unmistakable. Because a consensus on nomenclature had yet to be achieved, the disorder was still called by many different names. Rather than attempting to reconcile this philologic confusion, for the sake of simplicity, we will use the term "catamenial hematoceles."

Menstruation and lesions at autopsy One of the crucial breakthroughs by this group of French investigators was their confirmation of what had been suggested for centuries: monthly menstruation was unequivocally the direct triggering event that led to the onset of an endometriosis-like disorder, with all the attendant symptoms including severe pain and internal growths. In contrast to practitioners from prior centuries, these scientists made observations for the most part without reference to hysteria, and they clearly considered it a purely organic pathology.

Catamenial hematoceles, pelvic sanguineous tumors, and rectouterine sanguineous cysts These initial discoveries were made by a group of French investigators performing autopsies on women who had died from severe and sudden pain during menstruation (what appeared to be cases of ruptured ovarian cysts). After they noted the presence of blood throughout the peritoneum as well as the presence of pathologic growths, it became clear that a previously unknown disease was involved [69, 73].

Although the discoveries made by Vesling, Ruysch, and de Haen in the previous centuries were freely acknowledged by this group of French physicians, disputes over priority were rife in their own time, which makes it difficult to discern just who discovered what and when. Complicating matters was the fact that not everyone called the disorder catamenial hematoceles; others referred to the disorder as metrorrhagic hematoceles, retro-uterine hematoceles, pelvic sanguineous tumors,

blood tumors, rectouterine sanguineous cysts, and extra-peritoneal cysts to name but a few. All the same, the story appears to begin with Jacques Delpech, Joseph Recamier [75], Alfred Velpeau [69], Hippolyte Bourdon, Armand Trousseau, and Gustave Bernutz, all of whom were among the most commonly cited by their contemporaries as the first nineteenth-century investigators to report on catamenial hematoceles or their equivalent [69, 73, 76, 82, 83].

In 1830, Delpech noted a case similar to Ruysch's, in which a young woman diagnosed with menstrual retention presented with pain and some form of uterine lesions or tumors. She was found to have a vaginal obstruction disorder, leading Delpech to conclude, just as Ruysch had, that it was the extravasation of menstrual blood, in this case, the result of an obstruction that had caused pain and lesions [82]. Two years later, Recamier made similar discoveries and expressed surprise when "on making an incision to the posterior wall of the vagina for the purpose of evacuation of the contents of a supposed abscess discovered that instead of pus a copious discharge of black disorganized blood followed" [75] (Fig. 2.41). Meanwhile, from Velpeau's 1833 atlas of surgical anatomy, the postmortems of patients described as having hysteria, suffocation of the womb, dysmenorrhea, or who "had long been subject to abundant menorrhagia" revealed macroscopic similarities to endometriosis and/or

Fig. 2.41 Highly regarded French physician Joseph Recamier was one of the earliest in the nineteenth century to clinically and macroscopically describe cases with significant correspondence to endometriosis. (Reproduced with permission of the Wellcome Library, London. Portrait of J.C.A. Recamier by Auguste Corlieu, Centenaire de la Faculté de médecine de Paris: [1794–1894], published by Imprimerie Nationale, Paris, 1896, Image no. L0009737.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

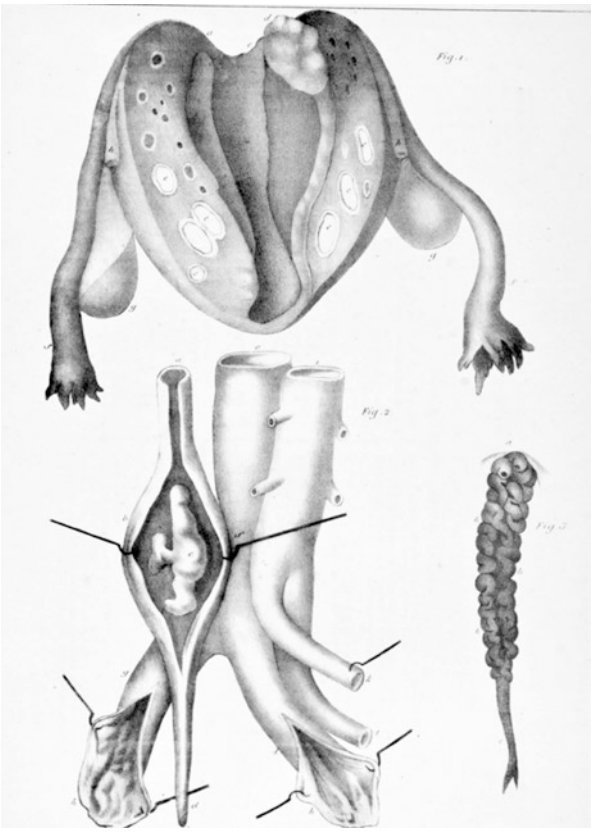


Fig. 2.42 Image taken from Armand Velpeau's 1833 atlas on surgical and pathological anatomy. Based on the textual and visual evidence, this image may represent a case of adenomyosis. (Reproduced with permission from Lane Library, Stanford University. A. Velpeau, *Illustrations of All the Most Celebrated Medical and Surgical Works: Comprising a Complete System of Morbid and Descriptive Anatomy*.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

adenomyosis [72, 84] (Fig. 2.42). Included among these various postmortem reports were cases of obliterated tubes, ovarian cysts containing "blackish vesicles, with a mucous tissue of the same colour," and uteri double the normal size and riddled with nodules [84].

Gustave Bernutz

The investigator who deserves a goodly portion of plaudits for ensuring that the menstrual connection was vigorously emphasized was Gustave Bernutz, whose groundbreaking 1848 treatise on this newly discovered disorder described nearly all the clinical and macroscopic symptoms associated with endometriosis, including the specific link with the onset of "violent" pain symptoms at menstruation as well as the appearance and disappearance of nodules in relation to the cyclic pattern of menstruation. In his excellent summary of his 1848 article (published in 1866), Bernutz wrote about "the long explanations entered into for the purpose of showing

the relation that exists between that form of intra-pelvic hemorrhage and menstruation" [73]. In a seemingly exasperated tone, Bernutz attempts to defend his (and Ruysch's) priority in discovering the disorder, explaining that "the trouble I have taken to prove that certain pelvic tumours originate in a disturbance of the catamenial function, and are the remains of former menstrual extravasations, I might certainly have constituted a prior claim to the merit of having discovered haematoceles. But in reality I make no pretension to that discovery, the merit of which, as I stated in 1848, belongs entirely to Ruysch" [73].

John Hughes Bennett and Antoine Viguès

At about the same time as Bernutz, the eminent physician and pathologist from Edinburgh John Hughes Bennett, who is better known as the first to describe leukemia in 1847, also reported on what he considered peculiar cases of metritis that arose at the onset of menstruation and produced swellings, globular tumors, interference with bowel and urinary functions, and what he believed to be pelvic peritonitis [81, 85]. At about the same time, Antoine Vigùes, who was cited as among the most influential investigators, wrote an 1850 article "Des tumeurs sanguines de l'excavation pelvienne, chez la femme" that was recognized even by Bernutz as exceptional and highly influential in bringing the subject of catamenial hematoceles to the forefront of study [86].

Armand Trousseau

To some degree, the nosologic debates were resolved when Armand Trousseau renamed the disorder "catamenial haematoceles" in 1858, after he had observed nodules and other symptoms that appeared and disappeared in conjunction with menstruation [76] (Fig. 2.43). Alluding to the extravasation of blood hypothesis, Trousseau reported that the disorder often "occurs in excessive menorrhagia or when there exists an accidental or congenital obstacle to the natural exit of blood from the uterus into the vagina" [76].

The *British Medical Journal* praised Trousseau's work not only for his new terminology, which more accurately described the condition, but also for his discussion of differential diagnoses, clearly distinguishing other varieties of lesions that formed as a result of injury or vascular aneurism [76]. In summarizing Trousseau's work, his British reviewer provides one of the clearest explanations of what amounted to fresh insights at the time, and also provides a rare firsthand account of just how little was apparently understood about menstruation:

> To explain the occurrence of catamenial hæmatoceles, M. Trousseau calls to mind the phenomena which occur in the uterine system during ovulation. Under the influence of the menstrual act, the whole uterus is in a state of congestion that may be seen by the speculum.

Fig. 2.43 Portrait of French physician Armand Trousseau, who coined the term "catamenial haematoceles" and was one of the earliest in the nineteenth century to clinically and macroscopically describe cases with significant correspondence to endometriosis. (Reproduced courtesy of British Medical Journal Publishing Group, Ltd. Archives of Disease in Childhood Fetal Neonatal, 1999; 80[2].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

> The neck of the uterus is swollen; the vagina, the labia majora and minora, are all in an evident state of erothism; and at the same time there is pain along the broad ligaments—a feeling of weight produced by the turgescence of the hæmorrhoidal vessels. This great flow of blood to the uterus is followed every month by a hæmorrhage. What is the seat of this? In general, Trousseau observes, the seat of hæmorrhage (at least in disease as distinguished from injury), is the mucous membrane. It is not probable that the blood descends each month with the ovum along the Fallopian tubes; for the disruption of the ovum is a process of enucleation, and cannot produce hæmorrhage; uterine hæmorrhage occurs either from the internal surface of the uterus, or from the interior of the Fallopian tubes. It now becomes very easy to understand the formation of catamenial hæmatocele.
>
> It is from the upper part of the Fallopian tube that M. Trousseau believes the blood in such cases to be derived. He does not think it possible, from the rapid coagulation of the blood in the vagina, that the fluid poured into the peritoneum can have passed upwards through the uterus and the tubes.
>
> This theory perfectly accounts for the monthly relapses to which women who have once had catamenial hæmatocele are subject. An excessive flow of blood to the uterine region and a special predisposition are sufficient to produce catamenial hæmatoceles at definite periods for an indefinite time [87].

The summary of Trousseau's specific cases provides an excellent enumeration of all the symptoms, which were now recognized as part of this specific new disease category. One woman's case held particular interest:

> Between two and three years ago, she had retrouterine hæmatocele each month, for four months. During two years, her catamenia were regular; but on March 14th last, she was

> admitted into hospital with an enormous hæmatocele, which disappeared, and appeared again at the monthly periods in April and May.
>
> When once the blood is poured into the peritoneum, it follows hydrostatic laws. The patient is obliged to lie down to relieve the pain which she feels; and the fluid gravitates to the lower and back part of the pelvis. It accumulates in the recto-vaginal *cul-de-sac;* then it passes beyond the ligaments into the iliac fossae; thence it ascends, and submerges the uterus. In M. Trousseau's patient, the effusion reached the umbilicus. This female presented also with a peculiarity which obscured the diagnosis: the hæmatocele was accompanied by a menorrhagia with retention, so that the uterus was excessively distended, and a round hard body was felt above the pubes, which M. Langier at first imagined to be a polypus. But, examining by the rectum, this surgeon (who had long known the patient) ascertained, as he had done before, the existence of an immense mass enveloping the uterus [87].

Trousseau also proffered treatment options:

> The affection then demands the ordinary treatment of menorrhagia; and, of all remedies employed in this malady, M. Trousseau confides in none so much as in cinchona … If the hæmatocele had reappeared, the patient would take dilute sulphuric acid and rhatany … The pain, in M. Trousseau's [patient's] case, was relieved by hemlock poultices, moistened with a mixture of belladonna and opium. This mixture consists of two parts of alcoholic extract of belladonna, and one part gummy extract of opium, with sufficient water to form a syrupy mixture … The [additional] treatment had consisted in taking a dracm of calisaya bark every third day, and a preparation of steel daily [87].

The reviewer also helpfully distilled Trousseau's diagnostic recommendations into one simple sentence: "Whenever a woman, at the monthly periods, complains of pain in the hypogastric region, and suddenly loses colour, catamenial hæmatocele may be diagnosed" [87].

Edward Tilt

Another British literature review published by physician Edward Tilt provided one of the most comprehensive overviews on the subject of catamenial hematoceles. Most importantly, Tilt's exhaustive enumerations establish that by the time of his work's publication in 1852, nearly all the symptoms and macroscopic findings we understand today to represent endometriosis had been identified and officially ascribed to one disorder. Tilt noted, for example, that catamenial hematoceles were known to be accompanied by painful bowel movements, bowel constrictions, and excessive bleeding [81]. As well, upon vaginal examination, the blood-filled nodules were found to be very painful when touched, and often appeared and disappeared in concert with menstruation, forming adhesions wherever they occurred that eventually would fuse the various pelvic structures together in a tangle of adhesions: in other words, frozen pelvis [69]. It also appears that a nearly universal agreement had been reached that the disorder's most salient features were its menstrual connection, painful symptoms, and production of globular, fluctuating nodules.

Dysmenorrhea Most impressively, Tilt relates that it was already common knowledge that patients usually had a history of experiencing both menorrhagia and dys-

menorrhea. It was noted, for example, that "in the majority of cases the patients had suffered from pain with period" so often that he considered it "one of the most important symptoms to look for" [69].

Advances in Diagnosing Clinical Symptoms

With microscopy still a fledgling new field, careful clinical observations continued to be of critical importance. In this regard, the French were again pioneers. For example, French patient histories were exceptionally thorough, which helped them realize that women with catamenial hematoceles were often returning to the hospital at each menstrual cycle. At these monthly visits to the hospital, the women presented with the same pain symptoms each time, which were described as "violent cramp-like pains in the lower belly" [69]. Some of these women were said to be in such agonizing pain that they would be bedridden and vomiting for several days; others would drag themselves to the hospital each month, believing that they were dying. Ńelaton, another French physician who was involved in these early discoveries, also found that his patients experienced similar episodes of incapacitating pain, reporting, for example, that one of his patients, "had been suffering for 4 years; nothing had given her any relief; she was forced to remain in bed all the time, and yet she had the appearance of perfect health" [88].

Rectovaginal cul-de-sac, iliac fossae, ovaries, fallopian tubes, bowel Two subsequent literature reviews, one by John Byrne [75] and another by Alfred M'Clintock [69], noted additional symptoms, including painful intercourse. As for the various locations at which the lesions could occur, it was observed that "the effusion generally appears in the rectovaginal cul-de-sac, whence it may extend into the iliac fossae" [76, 89]. However, it was also known that the lesions could present throughout the pelvic region, including inside the uterine wall itself, the ovaries, throughout the peritoneum, and on the bowel and bladder.

The disease's ability to mimic ectopic pregnancies by invading the fallopian tubes was also recognized. In an effort to help others distinguish between these two conditions, Trousseau described cases studies in which deaths from fallopian blood bursting into the peritoneal cavity had occurred "in two young women without any relation to conception or attempted abortion; death took place in both so rapidly that suspicions of poisoning arose, and led to judicial inquiries, in which there was not elicited any other cause of death except that which I have stated" [76].

Chronic and acute forms Three different forms of the disorder were noted: acute onset, intense, and chronic. In cases of acute onset, women died from what appeared to be burst ovarian endometriomas, as indicated by the dozens of descriptions that these early investigators reported from postmortem examinations.

Differential diagnoses Armed with this impressive array of credible new data, many began to question the countless disease categories that conspicuously resembled catamenial hematoceles. Every day, it seemed dozens of disorders were being added to the growing list of differential diagnoses.

Tilt noted, for example, that the nodules could sometimes be distinguished from regular fibroids by their softer feel, the common presence of a retroverted uterus due to adhesions, and the absence of encapsulation, which was noted to make their removal much more difficult [81]. Despite Tilt's accurate advice, misdiagnoses were said to occur frequently, even by those familiar with the disorder [69, 89]. One practitioner described the diagnostic difficulties, writing that it was "difficult to distinguish them from pelvic abscesses, especially when the broad ligaments are implicated" [89]. To help distinguish between pelvic abscesses and catamenial hematoceles, one physician suggested that the difference was the catamenial hematoceles' production of sudden epigastric pain at menstruation which would not last as long as an abscess nor would fevers ensue as normally occurred with abscesses [69, 81].

Ever frustrated at the chronic state of diagnostic disorganization, Bernutz continued to chastise those who made the "irrational" mistake of lumping into the category he had so painstakingly cleaned up disorders "so dissimilar as "extra-uterine pregnancies," "congenital imperforations," "menorrhagias," "ruptures of aneurisms," and "thrombus" [73]. By the 1860s, this list had grown to include hemorrhagic pleurisy [69], syphilis, ovarian dropsy, chronic metritis, and hemorrhagic ovarian cysts [81, 90].

Chronic metritis versus catamenial hematoceles The induction of chronic metritis into the list of differential diagnoses was an extraordinary advance, representing an overturn of thousands of years of thought. In fact, it was among the most significant discoveries of the pre-Rokitansky era, though medical historians have never identified it as such. As mentioned earlier, we deem this discovery significant because our research indicates that chronic metritis was among the most common disease categories, along with hysteria, that endometriosis had been lumped into for most of modern history.

Serving for centuries as a convenient diagnostic junk drawer for just about any elusive gynecologic disorder, metritis was indeed the same "inflammation of the uterus" that Soranus had written of 2000 years earlier as responsible for all the symptoms of suffocation of the womb, including dysmenorrhea, sudden onset of violent uterine contractions, vomiting, fainting from pain, and sterility. And, recall that Soranus's reports were nearly identical to those of Duff, who also described metritis as triggered by menstruation and causing violent pain, vomiting, uterine contractions, bowel and bladder symptoms, back pain, and prostration for days. Descriptions of chronic metritis from nineteenth-century sources were just as revealing [91]. One medical encyclopedia from 1855, for example, reported: "In most cases, indeed, of chronic metritis there is much suffering attendant on menstruation" [92]. However, the most substantial revelation gleaned from these historical texts was that one form of metritis would later be recognized as diffuse adenoma—and diffuse adenoma was the same disorder that Rokitansky microscopically discovered in 1860, which was later renamed *endometriosis* [93].

Hemorrhagic ovarian cysts As mentioned, others in this pre-Rokitansky era also suggested that catamenial hematoceles were the same as "hemorrhagic ovarian cysts," but this idea was somehow lost to ensuing generations. Karl Rokitansky's

1860–1861 microscopic findings finally confirmed the connection. Later, the father of endometriosis himself John Sampson also came to this conclusion, noting in his 1921 article that adenomyosis (i.e., endometriosis) and certain hemorrhagic cysts were in fact the same disorder, only manifesting in different areas.

Proposed pathogenesis and competing theories By this time, a variation of Ruysch's reflux theory as one cause of catamenial hematoceles was viewed as common knowledge. For example, Byrne in 1862 noted that "the escape of blood into the recto-uterine cul-de-sac of the peritoneum is a fact that has been so long and often clearly demonstrated as to leave no room for doubt" [75]. One crucial distinction was made: in contrast to Ruysch, many by now believed that menstrual blood could reflux into the peritoneum, even when there was no known vaginal obstruction. However, like Ruysch, they believed that the blood itself was the predominant irritant that caused the lesions, inflammation, and what they believed was peritonitis.

However, several other competing and equally compelling theories of causality were circulating alongside the reflux theory. Ultimately, this etiologic chaos contributed to the somewhat contradictory diagnostic profile that began to emerge. At the root of this confusion was the reflux model's inability to explain the disorder in its entirety; a vexing dilemma even today.

Vigorous sexual relations One of the most common alternative theories was that blood could enter the pelvis by other means, including via external injuries to the abdomen [81]. Other proposed theories would be considered quite peculiar by today's standards; for example, some believed the lesions arose as a result of sexual activity or that engaging in intercourse during menstruation could trigger the reflux of blood. Vestiges of the nymphomania concept were also still influencing beliefs as others suggested that the lesions could arise from "violent bodily efforts, intense mental emotion, over-fatigue" and "excessive or rude coition" [69].

Clinical observations: final thoughts All told, by the mid-nineteenth century there were, as Byrne noted, "too many articles on the subject to even be able to mention" [75]. Although most credit Rokitansky as the first to identify endometriosis, our research indicates that these French physicians from the early to middle nineteenth century were in fact the first to do so in modern times. Even more crucially, they achieved a broader understanding than even their late nineteenth-century counterparts, by establishing nearly consistent nomenclature and offering a sufficiently narrow set of symptoms that were identical to modern findings, including accurate differential diagnoses.

Other nineteenth-century investigators It is interesting to contrast these discoveries with the research that was still under way into the condition of hysteria. Had a comparative analysis been made, the similarities between catamenial hematoceles and hysteria would have been evident. At any rate, while the proposed etiologies continued to reflect a wide array of theoretic moorings, the clinical profile of hysteria remained remarkably stable, with multiple parallels to endometriosis. For example, Baron Ernst von Feuchtersleben of Austria, a contemporary of Rokitansky,

spoke of transient swellings throughout the body that occurred with hysterical outbursts [29].

However, German physician Wilhelm Griesinger (1816–1868) provided one of the most comprehensive pictures of hysteria as a disorder with nearly all the symptoms and signs of endometriosis. After years of study, he concluded that hysteria was aggravated by the onset of menstrual periods and that menstrual disorders were prevalent. Griesinger went on to state that pelvic disease was the most "exclusive cause of hysteria," and that local disease of the "genitals"—the ovaries and vagina—"were of the greatest importance in regard to prognosis and treatment" (T2h9u).s, Griesinger advised that all hysterical patients undergo pelvic exams [29]. Like Schrön and a handful of others from prior centuries, Griesinger also noted an apparent hereditary propensity for hysteria [29]. As for other symptoms indicative of endometriosis, Griesinger observed constipation, indigestion, and diarrhea. Similarly, the well-regarded German gynecologist Alfred Hegar (1830–1914) demonstrated his clear understanding that hysteria was an organic dysfunction and became one of the earliest to perform ovariectomies "in cases of intractable hysteria" [94].

Meanwhile, the foremost French psychiatrist Philippe Pinel, who would later be credited with laying the groundwork for Charcot and Freud, explained that the "violent" hysterical outbursts would start when a girl reached puberty; with each monthly menstruation, she would have hysterical outbursts along with "bowel and urination problems," with symptoms persisting for "3 or 4 days," after which the patient would return to normal. The same symptoms repeated at the next menstruation, during which time "the attacks renewed themselves with the same violence" [29].

Jean-Martin Charcot

Knowing that Pinel had identified menstruation as the triggering event of hysteria makes it all the more baffling that his contemporaries returned to the teeming quagmire of psychological explanations in search of exotic new clues. Yet this is exactly where we find the preeminent French psychiatrist Jean-Martin Charcot, who preceded and paved the way for Freud (Fig. 2.44).

Charcot's first exposure to hysteria is said to have been in 1862 when he visited the Salp̂etrìere, the infamous insane asylum outside of Paris (Figs. 2.45 and 2.46). There, "sandwiched in between the ward for incurables and the ward for epileptics," Charcot found an area reserved especially for women suffering from "hysteroepilepsy." As one historian described the scene, some of these women had been viewed as "problematical young females," who had been dumped at the Salp̂etrìere "by their exhausted families" [72]. Others described the patients in the hysteroepilepsy ward as "among the saddest at the Salp̂etrìere" and that "Dante's phrase 'Abandon hope all ye who enter here' might well have been written above the door" [77].

Fig. 2.44 A nineteenth-century painting depicting the renowned French psychiatrist Jean-Martin Charcot with one of his patients, a supposedly hysterical woman who has been put on trial for insanity. A diagnosis of hysteria could have led to ruinous consequences at the time, such as excommunication from family and community and involuntary imprisonment in a mental institute. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Andŕe Brouillet, titled "A clinical lesion at the Salpetriere," *Une lec¸ on clinique`a la Salp̀etrìere* [1887].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

After studying these patients for some time, Charcot eventually began postulating his own theories, finding in particular that ovarian pain typified the hysterical experience. To address this particular symptom, Charcot even devised a contraption called an "ovary compressor" designed to ease the pain [29]. Yet, even with all of the evidence pointing to a gynecologic cause, Charcot still concluded that hysteria was a psychological disorder. Before long, all the incriminating theories of the past were dredged up again, and women were accused anew of being mentally unstable, histrionic, and neurotically anxious. These theories continued to be accepted as valid partly because few could find any organic smoking gun [7].

Still, these fanciful ideas were not enough to stop the onward march of scientific medicine. The orthodoxies of old began to fall by the wayside, edging endometriosis toward its decisive moment of microscopic confirmation. Even the entrenched practice of bloodletting was finally being called into question [30]. Another pivotal event was the introduction of a microscope that actually worked. When key improvements were made to the microscope around 1826 by Joseph Jackson Lister, it was finally welcomed into the armamentarium of medicine. Meanwhile, the first tentative steps into endocrinology were also under way, with

Fig. 2.45 A rare image of a nineteenth-century vaginal hysterectomy being performed at the Salpetriere hospital, the renowned French institute for psychological disorders where women diagnosed with hysteria were commonly sent for treatment. (Reproduced with permission of the Wellcome Library, London. Painting by G. Villanova, "Operation for vaginal hysterectomy by Professor Segond at the Salpetriere Hospital, Paris, 1881." Image no. L0011589.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Bernard leading the way with his astonishing discovery in 1855 that the liver excreted sugar on its own [30].

Rudolf Virchow

The degeneration theory. In such a context, Rudolf Virchow, the renowned German pathologist recognized as the father of microscopic pathology, almost seems inevitable to the story of endometriosis (Fig. 2.47). As one medical historian put it, the conception of disease had once centered on Morgagni's organ, then on Bichat's tissue; and now, at last, we had Virchow situating disease in the essentially irreducible cell [30]. Indeed, by approximately 1855, Virchow apparently had discovered the same catamenial hematoceles as the French group, but unfortunately no one made

Fig. 2.46 A fictionalized image of a female patient in a straitjacket from Salpetriere hospital. (Reproduced with permission of the Wellcome Library, London. Engraving by Ambroise Tardieu described as "Insane patient in a strait-waistcoat," from the novel *Les maladies mentales* by Jean Etienne Dominique Esquirol, Paris, 1838. Image no. L0011302.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

this connection. Thus, Virchow and other German and Austrian investigators described conditions similar to catamenial hematoceles that were instead referred to as cystic adenomyomas, soft myxo-myomatous cysts, or soft adenomatous myomas or cysts [95].

In explaining the softer forms of myxo-myomas, Virchow suggested that these cysts developed from the adenoid tissue of the endometrium. In what would prove to be a powerfully influential idea, Virchow also asserted that these growths were examples of his widely accepted degeneration theory, which stated that regular fibroids could degenerate into multiple forms, including into these cystic types and sarcomas as well [95–97]. As it would turn out, Virchow's soft myxo-myomatous cysts would also be eventually identified as adenomatous myomas—which were later renamed endometriosis.

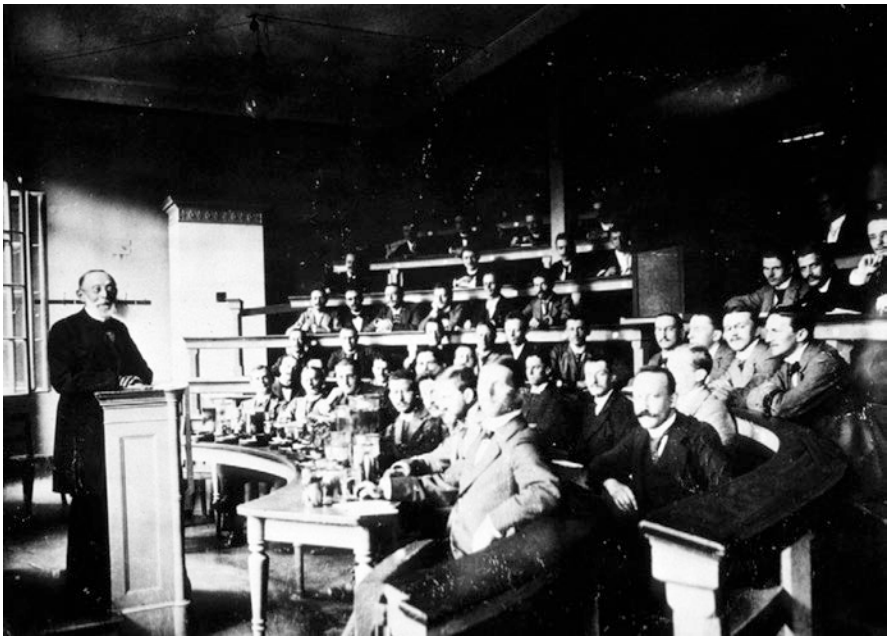


Fig. 2.47 Renowned pathologist Rudolf Virchow proposed his highly influential degeneration theory in reference to gynecologic pathologies with many similarities to endometriosis and/or adenomyosis, referred to then as cystic adenomyomas, myxo-myomas, or soft adenomatous cysts. (Reproduced courtesy of the U.S. National Library of Medicine, Call no. Portrait no. 21.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Karl von Rokitansky

Microscopic discovery of endometriosis When Austrian pathologist Karl von Rokitansky became the first to microscopically discover endometriosis in 1860, it was an exquisite synthesis of some of medicine's most salient developments: clinical pathology, microscopy, Bernard's endocrinology, Bichat's histology, Virchow's cell, de Graaf's ovary, Müller's reproductive tract, and Wolff's mesonephric ducts (Figs. 2.48 and 2.49). The newly improved microscopic histopathology technologies that had recently become available also helped Rokitansky realize that the endometrial-like glands and stroma he unexpectedly found in several tissue samples were aberrant growths and therefore constituted a previously unnamed pathology (Figs. 2.48 and 2.49).

Of course, other pathologists had access to microscopes and advanced histopathologic techniques. However, as endometriosis expert and historian Ron Batt noted, Rokitansky was "the age's champion dissector," and was therefore uniquely prepared for this moment by having performed at least 20,000 autopsies by Batt's estimate [30, 47]. Such extensive experience proved pivotal: after Rokitansky thoroughly examined a recently excised uterine polyp, a "fresh specimen from a live

Fig. 2.48 Portrait of Austrian pathologist, Karl von Rokitansky, recognized as the first to microscopically discover endometriosis when he observed the presence of endometrial glands and stroma in pathologic lesions of the reproductive tract. (Reproduced courtesy of the U.S. National Library of Medicine.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

patient," as Batt described it, as well as several other tissue samples stored from previous autopsies, he was able to perceive that "Some fibrous tumors of the uterus contain gland-like structures that resemble endometrial glands" [98]. It is this discovery of Rokitansky's that is now viewed as perhaps the most pivotal moment in the history of endometriosis. That year Rokitansky published his findings in an article titled "On Neoplasias of the Uterine Glands in Uterine and Ovarian Sarcomas [Uterusdrusen-Neubildungen in Uterus und Ovarial-Sarcomen]" [47, 98, 99].

By 1861, Rokitansky had identified even more phenotypes, such as benign, solid, and cystic intramural uterine "adenoids," benign solid polyps that invaded the endometrial cavity, and a third benign type that invaded the ovaries [47]. As for the ovarian type, he noted that "uterine-gland-containing sarcomas were also present in ovarian tissue sometimes leading to the formation of cysts," an observation that places Rokitansky as the first to microscopically detect that the two conditions derived from the same endometrial gland origin [98]. Despite Rokitansky's priority in this area, today most attribute the microscopic discovery of endometriosis of the ovary to either Russell in 1899 or Sampson in 1921.

Cystosarcomas Unfortunately, Rokitansky decided to use the rather misleading name "cystosarcoma" for the uterine polyps he had discovered, even though he

Fig. 2.49 Rokitansky with his fellow professors at the Vienna General Hospital. (Reproduced with permission of the Wellcome Library, London. Lithograph by J. Stadler, 1855, after A. Prinzhofer [1853], titled "Medical professors at the University of Vienna." Image no. V0006770.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

knew the condition was benign [47]. As Batt's research uncovered, Rokitansky chose the term "sarcoma" to designate the benign growths, not because of any especial analogy with muscle-flesh but in order to fix and define a name "familiarized by long usage" [47]. Some have discounted Rokitansky's work for using the term cystosarcoma. However, given the influence of Virchow's degeneration theory, it was an understandable decision. Moreover, even the early twentieth-century endometriosis pioneer, Cuthbert Locker, admitted that certain forms of endometriosis and other uterine growths undergoing "degeneration" were sometimes difficult to distinguish from sarcomas [100]. And, even today growths are sometimes referred to as benign neoplasia.

It is curious to note that even with the prodigious number of autopsies Rokitansky performed, he did not appear to recognize that the disease he was examining was already being referred to by dozens of other names. For this reason in particular, his work proved unexpectedly inadequate for reducing the nosologic confusion. Also, because Rokitansky worked exclusively as a pathologist, few clinical symptoms were mentioned in connection with his microscopic findings. This may have contributed to the difficulty others had in connecting Rokitansky's discoveries to their own clinical experiences. Indeed, with the exception of von Recklinghausen, who referenced

Rokitansky's work [47], it appears that other investigators continued to report on sanguineous cysts, catamenial hematoceles, ovarian hematoceles, soft myomas, and fibrocystic myomas with little mention of Rokitansky's cystosarcomas.

After Rokitansky

In addition to the terms already mentioned, lesions by dozens of other names that were described with similar endometriosis-like features continued to be referenced throughout the late nineteenth and early twentieth centuries, including intrapelvic blood tumors [84], hemorrhagic endometritis hemorrhagic periperitonitis, "continuous growth" polyps of adenomatous uterine polyps, hemorrhagic ovarian cysts, hemorrhagic pleurisy [69], peritoneal ovaritis, subperitoneal sanguineous effusions [101], ovarian cystomata 102), hysteritis, abdominal aneurisms [102], ruptures of Graafian vesicles [103], ovarian cysts of abdominal wall, hematic cysts, internal menorrhagia, hemorrhages of ovarian vesicles, peritoneal polypi, fibrous polypi associated with internal hemorrhoids, pelvic cellulitis [104], cystofibromata [105], polypoidal submucous growths, and polypoid cystic adenomyosis of the uterus. Based on our investigations of each of these disease classifications, they all shared significant similarities with endometriosis.

As for the French group's breakthrough research on catamenial hematoceles from earlier in the century, by the late nineteenth century, interest in the subject seemed to fade considerably. This may have been a result of the influential views of the renowned London physician Robert Lawson Tait, whose 1888 discussion of catamenial hematoceles categorically debunked the earlier ideas, claiming that all cases of intraperitoneal hematoceles were merely the vestiges of ruptured ectopic pregnancies [102].

It was this supremely disheveled scene that the pioneers who followed Rokitansky were forced to disentangle. Among the first to follow Rokitansky and enter this chaotic fray was Waldeyer who suggested in 1870 that ovarian "cystomata" could trace their pathologic origins to an invasion of displaced epithelium stroma [106]. In 1882, Babes from Budapest reported microscopic findings that described the presence of ectopic endometrial tissue in a specimen of uterine myoma [100, 107]. Remarkably, Babes also described the presence of one of these "uterus myotum" in a 91-year-old woman, one of the oldest patients with endometriosis to have been reported in the literature. In 1883, Diesterweg described blood-filled cystic tumors lined with ciliated epithelium, and Austrian gynecologist Breus described a 7-liter cystic uterine myoma also lined with ciliated epithelium [47]. In 1887, Johann Chiari became one of the first to report on the presence of microscopically confirmed endometrial tissue in the fallopian tubes, a disorder he called "endosalpingiosis" [100].

C. Schroeder

By at least the 1880s, if not earlier, some progress was made toward a consensus in nomenclature when Schroeder introduced the term "adenoma uteri diffusum." It was from this term that the acclaimed endometriosis pioneer Thomas Cullen and

others in the twentieth century would derive the modern term "diffuse adenomyoma," which Sampson in turn renamed endometriosis [93]. Schroeder's work also figured into the crucial reexamination of metritis, for the second time in the century. Specifically, in 1888, Schroeder proposed that some forms of metritis were not separate disease entities at all, but were in fact the same condition as "adenoma uteri diffusum" (i.e., endometriosis). In other words, Schroeder recognized that certain phenotypes of metritis were actually most likely endometriosis [93]. This critical breakthrough prompted others to reevaluate metritis in an entirely new light as well.

By the late 1880s, other diseases were added to the differential diagnostic profile of diffuse adenomyomas. During these investigations, poignant reports of the severe pain systems were recorded. In one article, for example, a woman diagnosed with diffuse adenomyomas was described as enduring pain symptoms that were "most severe during the first few days of the flow, but lasted through the whole time," and that "when the pain began she tossed about, groaning in agony, and often threw herself … on to the floor, where she rolled about in a most helpless state; she had twice threatened to take her own life in the despair of looking forward to the next menstruation" [108]. Many patients with endometriosis would probably agree that these descriptions come closer to capturing their experience of pain than the term "dysmenorrhea" ever could. Several authors now even admitted that some of their patients with diffuse adenomyomas were reporting that they had been experiencing "agonizing pain'' with menstruation since their teenage years [109].

Franz Winckel

In 1887, Franz Winckel became one of the first to note that women with endometriotic nodules that were small enough to escape notice were more likely to be classified as hysterical. Specifically, he observed that: [these women are] "simply called 'hysterical' because the tumors are still too small to be recognized by palpation, and the uterus may neither be enlarged, displaced, nor otherwise affected" [110]. He also indicated that the women's outward appearance of health was a problem, reporting that: "While at the same time, the patients are apparently strong and vigorous, it is one of their greatest sorrows that their friends seem unable to comprehend why they should complain."

Friedrich von Recklinghausen

These discoveries were certainly crucial contributions, but it was Friedrich von Recklinghausen who garnered considerable worldwide attention for his groundbreaking publications in 1893 and 1896 (Fig. 2.50). The latter monograph was particularly influential—or, as Cullen referred to it, "epoch-making" [72]. Von Recklinghausen's work stood out in part because he was among the first at the time to advance a sufficiently plausible theory to explain the origin of these unusual growths. Moreover, von Recklinghausen's new wolffian theory, named after the

Fig. 2.50 Portrait of renowned German pathologist Friedrich Daniel von Recklinghausen (1833–1910), who published highly influential works on endometriosis and advanced the Wolffian theory of pathogenesis. (Image courtesy of the U.S. National Library of Medicine. Published by J. F. Lehmann, Munich, Call no. Portrait no. 5608A.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

preeminent embryologist, Casper Wolf, represented an intriguing (if not entirely accurate) departure from traditional views about how pathologies arise. The tired, old ideas of yesteryear, implicating infection and inflammation, were retired from their service as explanatory precepts. Instead von Recklinghausen proposed that these growths derived from misplaced embryonic mesonephric ducts; in other words, they were practically preordained [47].

Although von Recklinghausen was not the first to advance an embryonic theory of pathogenesis (Breus had proposed his own a year earlier) and even though his theory would not pass scrutiny by later investigators, its introduction at this time served as a much needed catalyst for reawakening interest in the subject. His work also aided in the consolidation of nomenclature, as investigators around the world almost immediately abandoned their own terminology in favor of von Recklinghausen's newly coined term "adenomyomata" (a term used to describe various forms of endometriosis at the time).

Von Recklinghausen controversies One of the most acclaimed of von Recklinghausen's contributions was his new, if somewhat disputed, insights into the glandular elements found in endometriotic growths. As Cullen explained in 1908,

"Glandular elements have from time to time been noted in myomata and, according to Breus, Schroeder, Herr and Grosskopf were able to collect a total of 100 cases up to 1884. But not until the masterly work of von Recklinghausen, published in 1896, had this subject received much attention" [72].

Perhaps not surprisingly, it is this same crucial aspect of von Recklinghausen's research that has remained the subject of confusion, with some aspects still shrouded in ambiguity. In some histories, for example, it is suggested that von Recklinghausen completely failed to detect the glandular elements in the first place, or even if he did observe them failed to realize they were of endometrial origin, which is one of the most significant histopathologic features of endometriosis. Our review of the various sources reveals that although von Recklinghausen did observe glands and stroma in both intrauterine and extrauterine specimens, he assigned them to different origins depending on where the growths had arisen in the genital tract.

To understand how he derived this conclusion, we must reexamine the central tenets of the wolffian theory. First, it should be mentioned that the obsession with distinguishing between müllerian and wolffian tissue may well be a product of von Recklinghausen's era. During that time, embryonic studies were one of the most popular topics among pathologists; only within the previous 100 years had the different embryonic ducts from which the female organs differentiate been discovered, and they were the focus of many debates. It had already been established that the ovaries differentiate from the embryonic wolffian ducts, while the uterus, vagina, and fallopian tubes derive from the müllerian ducts. Because of these separate embryonic origins, von Recklinghausen concluded that endometriotic growths that occur in or near the uterus, vagina, or fallopian tubes are of müllerian origin, and that, therefore, the glands and stroma observed in these areas derive from an endometrial (uterine) origin. Because the ovaries trace their lineage to the wolffian ducts, he insisted that the glands observed in growths in or nearby the ovaries were separate entities, not of endometrial origin.

Von Recklinghausen clung to his theory in almost heroic defiance against the empirical evidence. This peculiar system explains many of the confusing contradictions that characterize von Recklinghausen's work, such as how he became one of the earliest (after Chiari) to microscopically confirm endometriosis of the fallopian tubes. He made this discovery while proposing that another disorder, salpingitis nodoso, was in fact simply another manifestation of müllerian-derived extrauterine adenomyomata, and thus with glands and stroma of endometrial origin [100]. Over the years, much has been made of this material misstep by von Recklinghausen. In the final analysis, however, it should be viewed as an entirely excusable lapse. This becomes especially apparent when one considers that his error was discovered by Cullen and others who had access to more advanced microscopy and histopathology technologies. Years later, Cullen made an effort to point out these extenuating factors. Cullen also made it clear that even with newer technologies, it was still difficult to distinguish between various tissues, noting that: "Sometimes the mucous membrane origin was easily proved, but in many cases not only were numerous sections necessary but in some instances a clear idea of the condition was obtainable only after an examination of very large sections embracing the entire uterine wall" [72].

After von Recklinghausen

Unlike Rokitansky's discoveries, which were offered without a compelling theoretical framework in which to make sense of his findings, von Recklinghausen's wolffian theory initially attracted some supporters, many of whom were his students. This may explain the increased enthusiasm for studying adenomyomata that occurred at the time. One preeminent endometriosis pioneer later even remarked that, despite the substantial flaw in von Recklinghausen's working model, he considered von Recklinghausen's work the critical contribution that placed diffuse adenomyoma on the map as a "real pathology" [100].

As endometriosis historian Batt has noted, it was also a time of "intense pathologic competition, with pathologists striving to have pathologic conditions named after them," which was perhaps another factor contributing to the flurry of research activity [98]. Duly inspired, dozens of new investigators headed straight for the fray of analysis, with many eventually offering their own theories of pathogenesis. For example, in 1895, the dystopic theory was introduced by Orloff, who described "glandular spaces under the serosa covering uterine myomata," which he considered to arise from "embryonic cells" [111]. Breus also advanced an embryonic cell theory of his own in 1894, one year ahead of von Recklinghausen's more well-known wolffian hypothesis [112, 113]. In 1897, Kossmann "demonstrated that the tube could supply gland elements and found that tubal adenomyoma was from accessory tubes," which advanced the theory that these growths arose from accessory müllerian ducts [114]. Russian physician N. S. Iwanoff proposed his own coelomic metaplasia theory in 1898, and one year later, Russell suggested that endometriosis "arose from Müllerian (paramesonephric) tissue" [112, 115, 116].

In 1896, German gynecologist William Freund of Strassburg contributed substantially to the much-needed clarification concerning the clinical symptomology by describing the physical symptoms most commonly reported by his patients. That same year, Pick reported that he had encountered endometrial tissue inside the ovaries of one of his patients [117]. Similarly, in 1897, Ries described endometrial tissue found in the lymphatic system. One year later, Russell reported being "astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue" [116]. By 1898, adenomyomata of the round ligaments had been reported by Bluhm [118]. Other investigators of this era included Babe, Ruge, Ribbert, Schottlander, Hauser, Strauss, Ricker, Martin [119], Orthmann, Baraban, Schroder, Werth, and Pilliet [100, 120].

Thomas Cullen

Of all the late nineteenth-century practitioners, it was Canadian-born, Baltimore-based Thomas Cullen who would achieve some of the era's most critical new insights. One of the earliest Americans to specialize in endometriosis and also well-regarded for helping establish the first gynecologic pathology laboratory at Johns

Fig. 2.51 Portrait of Thomas Cullen, America's first and most influential endometriosis specialist. (Reproduced with permission of Oxford Journals. *Human Reproduction,* 2004;19[4]:760–768.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Hopkins Hospital, Cullen holds a unique place in the pantheon of endometriosis pioneers for bringing all the disparate pieces together and formulating an exceptionally comprehensive clinical and histopathological picture of endometriosis (still called diffuse adenomyomas at this time) [121] (Fig. 2.51).

Cullen developed an interest in the disorder from the moment he microscopically observed his first case in 1882 [122]. However, the catalyzing moment for Cullen was when he realized that the world-famous von Recklinghausen had made an astonishing error by identifying some growths as having wolffian rather than endometrial (müllerian) origins. Only then did Cullen understand the significance of his own observations. Within 3 years of von Recklinghausen's initial article, Cullen published his own first article on the subject, which distinctly contradicted von Recklinghausen by emphasizing the disorder's mucosal origin [98]. Because Cullen could demonstrate that uterine adenomyosis "always could be traced to uterine endometrium," this meant that the wolffian theory was "impossible" [114].

Though the bulk of Cullen's work would occur in the twentieth century, by the end of the nineteenth century, he had already made significant contributions in

understanding the debilitating pain that accompanied the disorder, describing patients as undergoing "severe pain in the lower part of the abdomen" and "painful and profuse menstruation" [98].

Treatment Options in the Nineteenth Century

As in previous centuries, cultural norms continued to shape medical beliefs, and therefore treatment options followed the prevailing trends of the period. For example, in the so-called Victorian era of the nineteenth century, women were viewed as unusually delicate; thus, even well-regarded physicians like Lawson Tait suggested that young women with menstrual cramps should refrain from reading novels or listening to music as these hobbies were thought to cause overexcitement of their sensitive emotions, and thereby worsen their illness. Other cultural influences were not so harmless: for a brief time, clitoridectomies became a popular treatment for supposed cases of nymphomania (Fig. 2.52).

These of course are drastic examples of therapeutic extremes. However, more scientific treatment options were pursued as well. Approximately eight distinct patterns of care were promoted during the nineteenth century when endometriosis

Fig. 2.52 Image of an operating room from the late nineteenth century. (Reproduced courtesy of the U.S. National Library of Medicine. Described as "Instruction in Surgery. Scene in the Operating Room Amphitheater of the Massachusetts General Hospital, Boston Administering Ether to a Patient, 1888." Call no. WX 2 AM4 B7M4 No. 11 box 4 ins ovr.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

was either strongly suspected or (after 1860) confirmed through microscopic investigations:

1. No surgical intervention (remedies such as leeches, caustics, tincture of iodine, hot douches, sponge tents, ovary compressors, manual adjustments to the uterus, morphine, enemas, and/or orally ingested opiates, herbal medicants, or alcohol)
2. The twist-and-tear-off method
3. Puncturing/"tapping" growths
4. The "clawing out" method
5. Electrocautery
6. Dilation and curettage (D&C)
7. Oophorectomy, subtotal hysterectomy (abdominal and vaginal)
8. Partial excisions

No surgical intervention From the early to middle nineteenth century, before anesthesia and aseptic techniques were available, most physicians refrained from treating endometriotic surgically. However, this moratorium on surgery did not stop the development of invasive or painful treatments. In fact, aside from the milder prescribed therapies such as hot douches and morphine for pain, more invasive techniques such as bloodletting or the application of leeches to the cervix were practiced, some of which continued to be used up to the 1880s (Fig. 2.53). Indeed dozens of mainstream journal articles by well-regarded physicians demonstrate that leeches were considered a mainstay in treating any condition associated with menstruation (Fig. 2.54). To some extent, this form of treatment reflected that the spoiled menstrual blood theories, first proposed in Hippocrates' time, still held sway [108].

In one unsettling account, a practitioner advised others to be sure to count their leeches, as they had been known to occasionally wind up lost inside the uterus, a dreaded event by both patient and physician. Surely, anyone with a healthy imagination would conclude that losing one's leeches inside a patient's uterus was definitely not a good thing to do. Even so, the author felt compelled to clarify that a lost leech would cause not only considerable physical pain but undue mental distress for the patient [123]. Some attempts were made to discourage the use of leeches; Trousseau noted that leeches applied to the genitals led to "local disturbances" such as boils and that healing leech bites became itchy, which could "lead to bad habits" [76]. So central were leeches to nineteenth-century medical care that one medical historian found that they represented 4% of one London hospital's budget; Meanwhile, France was, at one point, purportedly importing 33 million leeches each year [30, 123, 124].

A variety of concoctions for ingestion, often of unknown or questionable ingredients, also continued to be popular. Pinkham's Vegetable Compound, one of the most successful of these patent medicines, even had its own catchy tune: "Elsie W. had no children \ There was nothing in her blouse \ So she took some Vegetable Compound, \ Now they milk her with the cows" (Fig. 2.55). Even medicinal marijuana found its way into the story of endometriosis: Queen Victoria's doctor, Sir John Russell Reynolds, was said to have prescribed her "monthly doses of Cannabis" throughout her adult life.

Fig. 2.53 For centuries, bloodletting was routinely practiced and was among the most common treatments prescribed throughout the ages for women with endometriosis-like symptoms. (Reproduced courtesy of the U.S. National Library of Medicine, "La Tout Par Precaution/N. Guerard inv et fecit." Call no. WZ 336 G92 no. 1 sol.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Other nonsurgical but nevertheless invasive techniques included the internal and external application of caustic styptics. These substances consisted of materials such as perchloride of iron, nitrate, or mercury-based compounds, which were applied directly onto the inner surface of the uterus or anywhere else that lesions could be felt [69]. Sponge tents designed as cervical dilators to relieve severe menstrual cramping were also in fashion for much of the nineteenth century. However, many practitioners complained of their popularity because of the serious uterine infections caused, all without any clear benefit.

One of the more peculiar (though decidedly more innocuous) treatments was the practice of repositioning uteri, which were thought to have become displaced. Many patients would present to their doctors with pain symptoms they believed to be from a displaced uterus. Patients commonly believed that uterine displacement could be caused by a strong jolt during a carriage ride on a bumpy road or from rough horseback riding. In one such case, the patient presented to her doctor after a riding

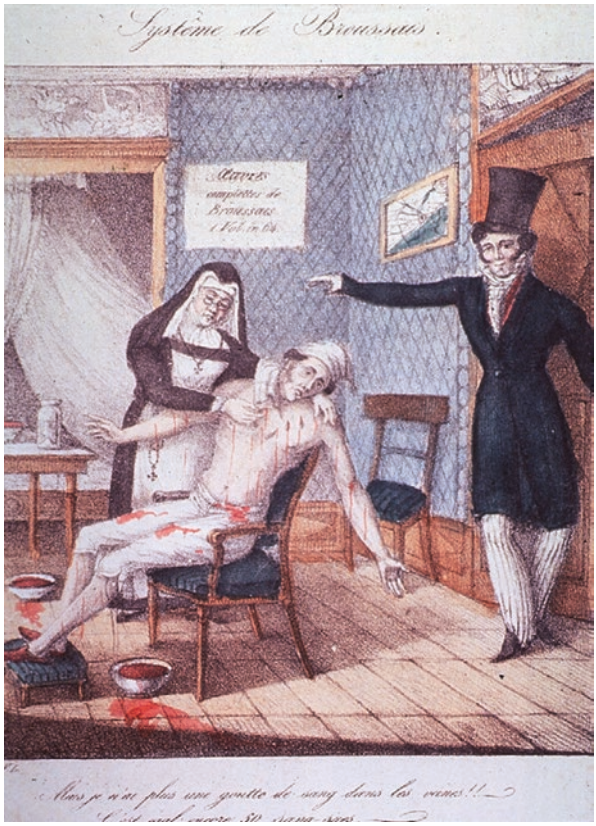


Fig. 2.54 Until the late nineteenth century, the insertion of leeches inside of a woman's vagina and uterus was routinely prescribed for patients with endometriosis-like symptoms. (Reproduced courtesy of the U.S. National Library of Medicine. Call no. WZ 336 Z55 no. 42.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

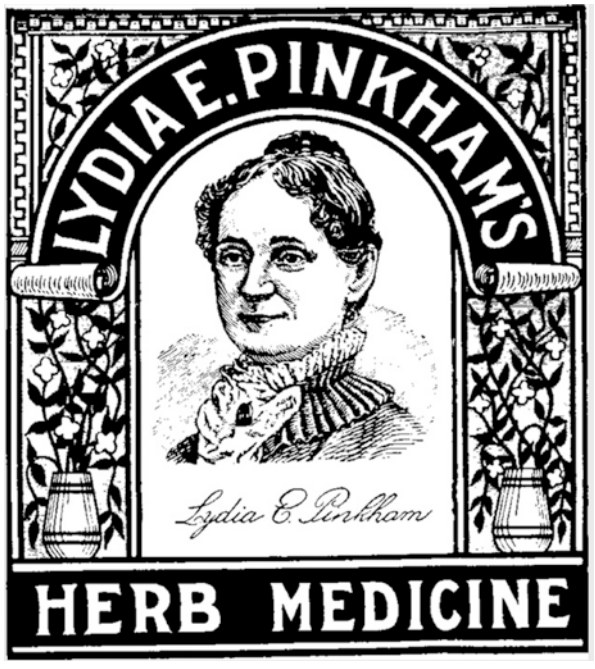


Fig. 2.55 Mrs. Lydia Pinkham's Vegetable Compound, a popular alternative medicine used by women throughout the late 19th and early 20th centuries for gynecologic and other conditions. (Reproduced courtesy of Wikipedia, http://en.wikipedia.org/wiki/File:Lydia_Pinkham.png.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

accident in which she believed her uterus had become misplaced; the doctor said that the patient reported all of her symptoms vanished after he had manually repositioned her uterus. Of course, it is quite possible that healthy retroverted uteri were also treated in this manner and blamed as the cause of many uterine disorders.

The practice of repositioning inspired other unfortunate variations. The least invasive and presumably least painful was the method in which the physician would manipulate the uterus manually by actually "pulling and tugging" on it in an attempt to move it to a presumed normal position. Other methods involved specially devised instruments such as the intrauterine repository, which was worn by a patient to pull her uterus out of its backward sliding ways and restore it to its presumed correct position. As with the sponge tents, because these intrauterine devices often caused severe infections, they were abandoned as soon as the surgical arts became safer in the late nineteenth century.

Humoral-based ideas still influenced treatment options as well, as can be inferred by the many purging emetics and enemas still being lavishly prescribed. Physicians were aware that many of these medicines were all but unbearable for their patients. One doctor recommended "a mixture of dilute sulphuric acid and turpentine" but discovered that "the women that can bear to take this atrocious compound are few and far between."

For milder cases, traditional palliative care was recommended, often in the form of alcohol, opium, or morphine for the pain. Outside mainstream medicine, folk remedies continued to be peddled, which comprised dubious ingredients with even murkier side effects. One such famous remedy prescribed specifically for hysterical women was Hoffmann's soothing liquor—its main ingredient was ether, which no doubt must have led to disastrous consequences at times [40].

Twist and tear off For any growth that protruded enough to be ligated, the twist-and-tear-off procedure could be employed. However, this method was also known for its high mortality rate.

Tapping and Puncturing

The introduction of anesthesia by the mid-century made attempts to puncture the nodules feasible, through either vaginal or abdominal approaches. The mortality rates, however, were reportedly as high as 70. After one member of that early group of French investigators lost a patient by this method, he strongly urged others to attempt puncture techniques only in cases when the lesions interfered with bowel function [81]. The introduction of trocars as a safer means for puncturing was also suggested; one source noted that "puncture with a trocar" was preferred to the "incision with a bistoury." However, even this safer method had its pitfalls. A surgeon named M. Monad attempted this procedure for what he thought was a simple case of a displaced uterus. It was too late when Monad realized that the patient actually had "peri-uterine sanguineous tumors (i.e. most probably endometriosis)." When he

punctured this growth with the trocar, it caused an "effusion of blood into the utero-recto pouch" and the patient died of peritonitis [69].

Clawing out From about the 1850s to 1870s, some dug out the nodules with blunt scissors or even with their own fingernails. To control the hemorrhaging that invariably ensued, packing and draining were attempted. However, these efforts usually proved useless and many died from blood loss or infection. In 1874, the renowned gynecologist James Marion Sims used this fingernail-clawing technique on an infertile patient with severe menstrual pain who subsequently died. Sims believed this outcome occurred because he misdiagnosed the patient with regular fibroids, a condition that he had successfully surgically treated numerous times. It turned out, however, that the patient had cystic myomas, the same growths that Rokitansky had identified as endometriosis. Unbeknownst to Sims, endometriosis was infinitely more difficult to surgically excise than regular fibroids. As a result of this completely unexpected outcome, Sims emphatically warned that attempting to surgically excise endometriotic nodules was too dangerous unless severe hemorrhaging was occurring. This is one of the earliest detailed accounts we have found of a patient with endometriosis dying as a result of surgical intervention [125].

Electricity Applying electrocautery directly onto the lesions was also used briefly in the late nineteenth century. By mid-century, after galvanization techniques were introduced into medicine, electric shock treatment was also used on women diagnosed with hysteria [40].

Dilation and curettage Blindly applied dilation and curettage methods were deployed routinely soon after Recamier introduced an improved instrument and method for this purpose [126, 127]. Recamier himself used this technique on the catamenial hematoceles he came across, incising through the posterior cul-de-sac.

Oophorectomy After the success of McDowell's ovariotomies became known in medical circles throughout the world, many brave pioneers—both patients and physicians—began tentatively experimenting with this procedure for severe cases (those thought to be ovarian cancer for example). One medical historian estimated that at least 200 ovariotomies were performed in England between the years 1838 through 1855, before the widespread use of anesthesia and before the introduction of aseptic techniques [30]. However, although McDowell reported only a 38% mortality for his own career total of 13 procedures, estimates from other sources indicate that mortality rates were as high as 75% for the average nineteenth-century physician [128].

Abdominal hysterectomy partial myomectomy With the introduction of aseptic techniques, surgery came to be seen as one of the most promising forms of treatment for women's disorders. This was especially true after the 1880s: when aseptic techniques had finally been universally embraced, death rates were reduced to more acceptable levels. Within this surgical milieu, hysterectomies and myomectomies became preferred treatments. In fact, in 1883, Diesterweg became one of the earliest to suggest total hysterectomy for patients with endometriosis [129].

Attempts to remove nodules via procedures similar to a myomectomy were already understood to be highly risky and ineffective in the case of fibrocystic myomas (as mentioned, now identified microscopically as endometriosis). As one physician warned, "the termination of the cystic fibromyoma is widely different from that of the simple [fibroid and leads] … to the destruction, sooner or later, of the life of the patient." In any case, it was eventually realized that simply excising the nodules or removing the ovaries was not enough to prevent the disorder from returning. Therefore, physicians began recommending hysterectomies.

Given the dangers of surgical interventions, it is not clear why doctors or patients took on these risks. One explanation might be the widespread belief in Virchow's degeneration theory: that is, these risky surgeries were performed not only by the woman's request to relieve pain and preserve her reproductive function but also because it was generally assumed that these growths would eventually degenerate into cancer. One physician of the era expressed precisely this sentiment when he recounted trying to remove nodules in the belief that they might turn cancerous and lost his patient as a result. Hence, physicians began demanding that a common nomenclature be established because each type of growth called for distinct surgical strategies: the right approach applied to the wrong lesion was potentially disastrous.

Surgeons Versus Traditional Physicians (Internists)

The astonishingly high number of surgery-related deaths did not go unnoticed by nonsurgeons. Indeed, some of the most heated debates in medicine arose during this era as medicine transitioned from strategies of expectant treatment to those of aggressive surgical intervention. One internist author lamented the growing disuse of conservative methods in favor of surgical interventions, derisively remarking that such conservative approaches had "once more been forgotten by those modern surgeons who deem knife using surgical science" [130].

By the mid-century mark, when death rates for most gynecologic surgeries were still as high as 50–70%, skepticism was certainly understandable. Some even went so far as to refer to the newly introduced "ovariotomies" as akin to murder [128, 131]. The methods surgeons used to reduce infections must have also been viewed as shocking departures from traditional medical care. For example, in these preantibiotic days, when aseptic techniques were still not entirely perfected, regulated, or accepted, it was a common practice for surgeons to pour hot distilled water into the abdominal cavity as a means for preventing septic peritonitis.

Methods that appeared to be even remotely invasive were also hotly contested. Even the newly introduced custom of routinely performing vaginal inspections with a speculum was debated. This practice, first initiated by French physicians, caused great outrage in British and American medical circles. In fact, for most of the nineteenth century, few physicians in Britain and America performed vaginal examinations of any sort, as they believed it to be too much of a violation of decorum [30, 124]. These specula wars led one British physician to go so far as to suggest that

French women were practically lining up to receive what he perversely imagined were gratifying speculum inspections. As he stated in 1838, "Our notions of modesty may be … out of date. Yet I trust that some time will elapse before OUR wives and daughters will distinguish themselves in this free and easy style" [124].

Conservative and minimally invasive approaches Dodging salacious accusations has never been fun, but the real vexing issue that surgeons and patients faced was the fact that mortality rates were still very high by modern standards, "regularly exceeding 70, even in the hands of the most eminent surgeons." The mortality rates for hysterectomies in particular were so high that the procedure was formally condemned by the Academy of Medicine in Paris in 1872.

Mortality rates Even though by the latter half of the nineteenth century, mortality rates had improved from the mid-century highs of 75, the incidence of mortality was still disturbingly high, leaving room for different approaches to be considered. For example, early attempts at partial excisions were being performed at least by 1852, though even in these more conservative cases recovery was not guaranteed. In an example offered by Tilt, a misdiagnosis similar to the one made by Marion Sims proved similarly disastrous for one Parisian surgeon, who "opened up the womb thinking to get out a fibrous uterine tumor" but instead found a catamenial haematocele, which again was known to be difficult to excise. As Tilt goes on to explain, the patient bled to death "because the artery was cut" [81].

With such consequences looming in the background, surgeons were desperate to find safer alternatives. By the 1880s, modest improvements to excisional techniques were made. For example, in 1888, Byrne describes his partial excision technique as a "case of pelvic haematocele cured by operation" [101]. By the 1890s, Cullen was performing similar procedures in which only certain portions of the endometriosis would be excised from the uterus through an abdominal incision [132]. From these examples we can see that nineteenth-century practitioners were clearly interested in performing surgeries in the most minimally invasive way possible, a 100-year head start on those of us who thought we were the ones to initiate this revolution.

Vaginal hysterectomies With the pressure mounting to reduce mortality rates, vaginal hysterectomies were reintroduced as a presumed safer alternative to abdominal surgery. Osiander of Germany had already achieved the first modern-day vaginal hysterectomy by 1801. Langenbeck and others, especially French physicians, soon followed suit. Yet the method fell out of favor again, most probably as a result of its difficulty but also because new technologies and techniques were introduced that made abdominal surgeries somewhat safer.

Just as has been the case in modern times, the two approaches competed for attention. Despite its recognized difficulty to perform, the vaginal method was appreciated for its considerably lower risks. It was known to be associated with lower mortality, with some surgeons reporting rates as low as 15% in 1886, and somewhere between 2% and 10% by the late nineteenth century. It was also touted for its fewer postoperative adhesions and complications and faster patient recovery.

Patient preferences During this time of immense upheaval in medicine, an important trend could be seen emerging: the hitherto nearly soundless, formless beings known as patients began asking questions and demanding answers. An article from 1896 provided the first hints that this trend was on the ascendant. The central issue addressed in the article concerned the dilemma that one doctor faced in deciding how to perform hysterectomies. He admitted that his own preference was for the abdominal route. However, his patients were so keen to avoid that method's large abdominal incision that they were pressuring him to perform the more demanding vaginal procedure, an approach that he admitted being ill-prepared to pursue. What a familiar dilemma this was; indeed, it what a startling reminder of history's recursive nature to see that the same sorts of dialogues that arose after videolaparoscopy was introduced had occurred a hundred years before.

Even though minimally invasive techniques were finally becoming available again, this did not exactly catalyze a wholesale departure from the older methods. One report from 1893 demonstrates that tapping was still being deployed: the surgeon explained that the untappable type of nodule, fibrocystic myoma (i.e., endometriosis), was "tapped by mistake" and that "the patient died of septicaemia from suppuration of the tumour" [133].

Final reflection on the nineteenth century In other disciplines of medicine, endoscopic techniques figured prominently in the treatment of some of history's most well-known figures. In one famous instance of endoscopy going awry, the technique was even implicated in the downfall of an empire, the one that Napoleon Bonaparte's nephew was trying to rebuild. Yet among the hundreds of articles reviewed for this historical overview, other than a brief, vague account mentioning Howard Kelly's use of air cystoscopy in 1896, we found no evidence in the English language literature of the nineteenth century to suggest that endoscopic techniques were being applied to diagnose or treat any gynecologic conditions.

The Twentieth Century

By the opening hours of the twentieth century, advances in multiple scientific arenas had already been achieved that would eventually figure prominently in the story of endometriosis. For example, the field of gynecologic laparoscopy was burgeoning, with Kelly, Ott, Bernheim, Orndoff, Short [134], Case, Hope, Fervers, Boesch, Anderson, and Benedict among the earliest to perform minor therapeutic and diagnostic laparoscopies. On the endocrinologic front, by 1895, Robert Morris had performed the first successful ovarian transplantation in a rodent, which helped bring the elusive workings of reproductive endocrinology into sharper relief [135]. Meanwhile, the new discipline of histology was on its way to becoming an indispensable diagnostic tool, especially after the introduction of modern specimen—slicing technologies which transformed it almost overnight into an infinitely more accurate methodology.

Mental Illness

There was just one small problem, however: these fancy advances availed surgeons nothing in the face of a seemingly invisible pathology. Indeed, it would be an abiding irony of modern medicine that all the advanced technologies in the world—the exquisitely calibrated microscopes, the penetrating eyes of X-rays, lasers, loops, logarithms, longer and better incisions—would all prove powerless against the supreme inscrutability of invisible lesions governed by an unfathomable array of molecular mechanisms. Yet modern medicine was expected to outwit disease states; when no lesions were found at surgery, practitioners shifted their focus back to the patient's mental status; 4000 years of science and searching, only to arrive back to this.

It was the unseen saboteur of the century. By the early twentieth century, significant milestones had been achieved nevertheless. After having captured the attention of such widely respected authorities as Rokitansky, von Recklinghausen, and Cullen, the signature symptoms of endometriosis (still known most commonly as adenomyosis or diffuse adenomyosis) had apparently become fairly well-known, at least in English language and German medical publications. In a rush of optimism, endometriosis specialist W. P. Graves reported in 1906 that so much awareness had been raised about the disorder that "even hospital attendants" were suggesting it to doctors as a possible diagnosis [120, 126]. Meanwhile, a new generation of investigators hastened the search for answers, such as Robert Meyer, who uncovered crucial new evidence in support of Iwanoff's coelomic metaplasia theory. In 1907, Meyer would also become the first to perform a bowel reanastomosis for the treatment of endometriosis [126], all without the benefit of antibiotics or other modern conveniences. Other early twentieth-century endometriosis researchers of note were Hirst [136], von Franque [137], Pick, de Jong, Mahle [114], MacCarty, and Graves [138].

Atypical Clinical Experiences

It was already known that endometriosis could arise in different regions of the pelvis, but researchers were only now realizing that symptoms could also manifest in vastly atypical ways. Jasche was one of the earliest to describe these anomalies, reporting in 1909 that some cases involved uncommon symptoms such as "no sterility, no peritonitis, no pain, no dysuria, and no local pain" [100]. Additionally, in 1918, English endometriosis pioneer Cuthbert Lockyer published his well-respected, widely referenced textbook *Fibroids and Allied Tumors*. Along with Meyer and Cullen, Lockyer was among the earliest to perform bowel resections on a patient whose bowel lesions were deeply infiltrating into the mucosa, which had been causing "diarrhea, defecation very painful, constipation and obstruction up to 3 weeks" [100]. This form of extensive bowel endometriosis had rarely been seen, and both Lockyer and later Cullen incorrectly believed theirs were the first cases in which endometriosis had invaded the mucosa of the rectum.

Thomas Cullen

As advanced as both Meyer's and Lockyer's accomplishments were, it was the work of Thomas Cullen that continues to stand out throughout the 1900s. Having observed his first case of endometriosis in 1882, by the beginning of the new century, Cullen had the advantage of 20 years' worth of experience on which to draw. After publishing on 22 cases of endometriosis in 1903, Cullen found his interest still piqued: "Since then I have paid especial attention to these growths and have been astonished at the striking frequency with which they occur" [72]. Indeed, Cullen became a fount of new insights; he was the first, for example, to recognize the need to remove the appendix as a prophylactic treatment for endometriosis patients. Cullen's years of experience in the laboratory where he obtained extensive knowledge of histology and pathologic anatomy also paid off, helping him become the first to realize that endometriosis could invade pelvic nerves, a process causing patients "excruciating pain when the pelvic nerves are invaded and then menses comes" [47]. One such patient of Cullen's experienced such severe menstrual pain that he felt "it was necessary to keep her under the influence of chloroform" [72].

Cullen's meticulous microscopic investigations were arguably the most crucial of the era for reducing the confusion concerning the histopathological features of endometriosis. To address any lingering doubts, Cullen made it clear that the defining microscopic features of endometriosis were the presence of glands that were "invariably surrounded by the normal stroma of the mucosa." But, in a conspicuous departure from von Recklinghausen's theory, he asserted that these glands always derived from an endometrial origin. Without these crucial clarifications, it would have been difficult to re-establish a stable definition of endometriosis given the growing theoretical discord that had ensued since the introduction of the müllerian and wolffian theories in particular [72].

Kidney damage Cullen was among the first to report the severe kidney damage caused by endometriosis encircling the ureters. Just as some other pioneers from the previous century had suspected, Cullen recognized early that even total hysterectomy did not ensure the disease would be cured. Cullen also provided some of the best descriptions of the disorder's ability to render the anatomy into frozen pelvises, which he said appeared as if all the organs had been sealed into one solid mass by the powers of some biologic glue [126].

Demonstrating his gifted surgical skills, Cullen was again one of the earliest, after Meyer, to perform bowel resections and to advocate surgical intervention for bowel endometriosis, warning of the great danger it posed if left untreated. He pointed out that endometriosis-induced intestinal obstruction could cause some patients to become chronic invalids, and in some cases would "undoubtedly lead to her death" (Fig. 2.56).

Morbidity and mortality Even after experiencing devastating surgical losses, Cullen continued to believe that the potential for intestinal obstruction was the far greater risk if it was left untreated. Bowel resections were known to be one of surgery's most difficult operations and were associated with high mortality rates, so

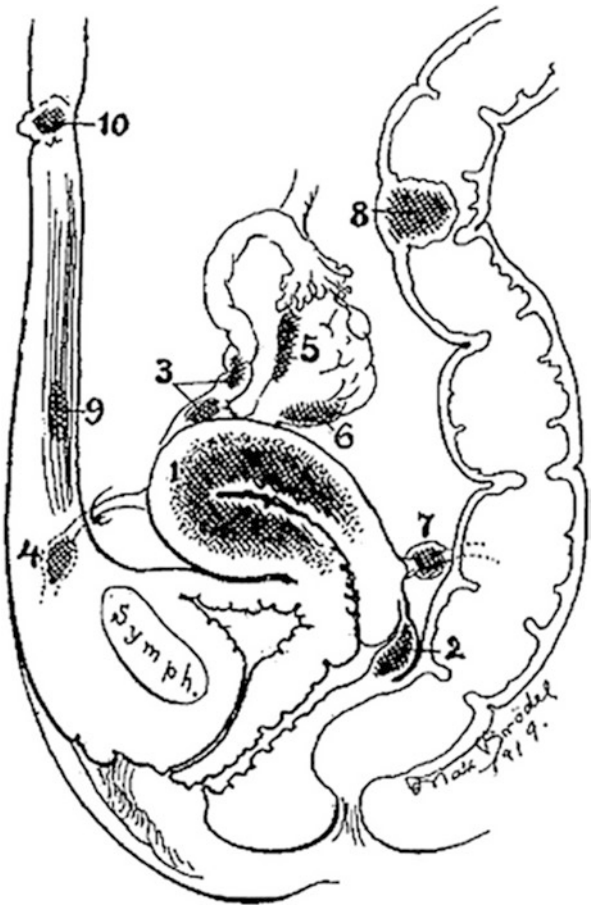


Fig. 2.56 An image of endometriosis of the bowel from Thomas Cullen's 1920 article. *The distribution of adenomyomas containing uterine mucosa*. (Reproduced with permission of Oxford Journals. *Human Reproduction,* 2004;19[4]:760–8.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

Cullen's continued advocacy was viewed by his contemporaries as highly controversial. Even so, he remained a vocal proponent of the procedure's use in serious cases. He was, however, quick to acknowledge the difficulty of these surgeries, stating that "without equivocation bowel surgery is infinitely more difficult than [even] hysterectomies for carcinoma" [126].

Predictably, most of Cullen's patients died from these surgeries. In some cases, he was forced to perform back-to-back laparotomies because, as he explained, his patients did "worse and worse" after surgery. Other adverse outcomes would ensue months later. In one unusually delayed reaction, 5 months after the first bowel surgery, his patient returned presenting with abdominal pain and vomiting. Cullen would later report that "they couldn't figure it out until it was too late." No blood had been coming from her stool, so they reasoned that it was probably nothing too serious. Therefore, an expectant approach was taken. She was recovering in the hospital from these symptoms after having received opiates for the pain, when, without warning, the "patient fell over, gasped a few times and died." It was only at autopsy that Cullen uncovered the reason: adhesions had encapsulated her bowel into loops of unrecognizable strangulated sections.

Ever alert for other disorders that endometriosis may have been mimicking, Cullen also offered crucial insights concerning differential diagnoses. He was one of the earliest, for example, to directly suggest that presumed cases of pelvic inflammatory disease were in fact endometriosis, stating in 1918 that "when early operation is performed in these cases, a certain number of our 'mild pelvic inflammatory cases' that heretofore have gone from bad to worse will be cured" [126].

Evolution of surgical approaches In the face of such unpredictable outcomes, Cullen's treatment approaches clearly went through stages of evolution as his understanding of the disorder's complexity grew over time. For milder cases, he recognized that a minimally invasive approach involving localized excisional techniques was sufficient. For those cases that had progressed beyond the stage where selective removal was effective, Cullen recommended subtotal abdominal hysterectomy with bilateral oophorectomy, stating that "for the diffuse variety, nothing but total hysterectomy should be performed."

As for techniques, Cullen suggests abdominal entries for severe cases, owing to the fact that the vaginal route is often impassable and riskier when the uterus is completely fixed to other organs or when the adnexa are inflamed. In all, Cullen's contributions profoundly impacted the course of events in the history of endometriosis. His publications were particularly influential, especially his 1908 masterpiece, "Adenomyomas of the Uterus," which Sampson acknowledged as a crucial factor in catalyzing his interest in endometriosis.

After Cullen, before Sampson Despite Cullen's breakthrough discoveries, and although there were now many new investigators in endometriosis research, the disorder still generated a great deal of confusion, and dozens of names were applied to the same condition, because sustained, widespread interest in the subject of endometriosis had failed to fully materialize. Many misconceptions were being circulated at this time, even though hints as to their inaccuracy were showing up in the literature. For example, despite dozens of case studies in which patients clearly explained that their symptoms had existed since their teenage years, there were still reports suggesting that the average age of onset was age 41.

Disappointment over the limited number of efficacious treatment options was also already evident as early as 1918, when even Lockyer remarked that "there is no doubt that curetting and medical treatment make matters worse." Another physician from 1918 expressed dismay at the difficulty of definitively diagnosing the disorder, lamenting "how is a clinician to decide what can only be found out by the knife and anatomy?"

John Sampson

Even with the tremendous insights gained over the last few decades, the fact remained that the state of knowledge concerning endometriosis amounted to no more than a speck of dust when compared with the vast universe of lingering unknowns. The void was waiting to be filled. This is why the searing lucidity that characterized John Sampson's works was greeted with such an effusion of enthusiasm from all around the world; his research filled the void by offering fresh new

insights and the promise of more to come (Figs. 2.57 and 2.58). Known today as the "father of endometriosis," Sampson was, in many ways, a very peculiar and exceedingly private man. His contemporaries recognized him as a gifted and meticulous

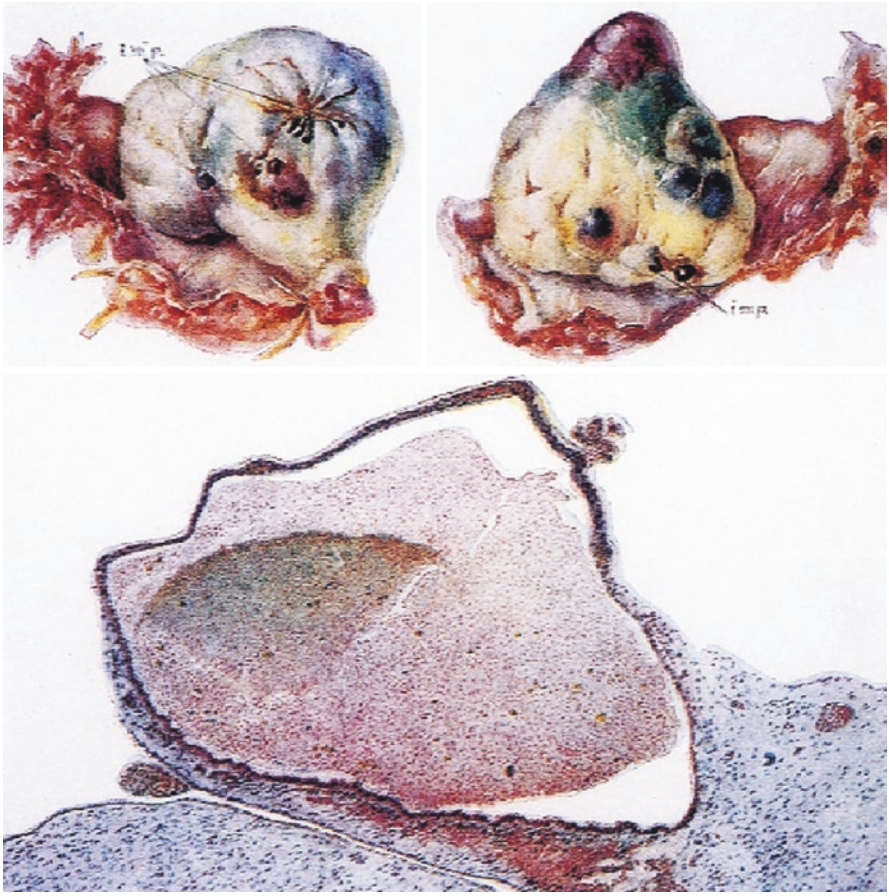


Fig. 2.57 Drawings of endometriosis specimens from John Sampson's seminal works of the 1920s. (Reproduced with permission of Wolters Kluwer Health. *International Journal of Gynecological Pathology,* 2001; 20[10].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

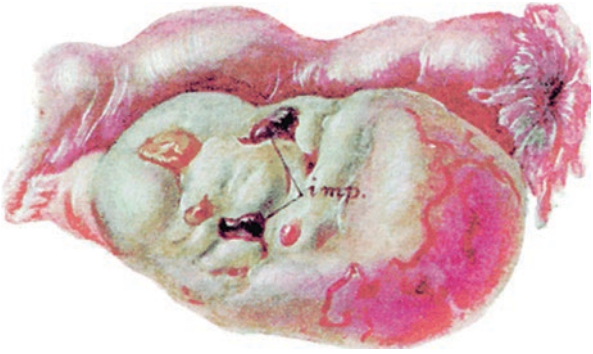


Fig. 2.58 Drawings of endometriosis specimens from John Sampson's seminal works of the 1920s. (Reproduced with permission of Wolters Kluwer Health. *International Journal of Gynecological Pathology,* 2001; 20[10].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

surgeon, but others saw him as more of a "severe task master." Whatever the case, it is evident now that Sampson's uncompromising ways and exhaustive precision figured into his research papers, which were densely packed with exceedingly intricate descriptions and averaged 79 pages long.

Sampson's article from 1927 is the most well-known, but his publications from 1921 and 1922 contain equally important discoveries, including allusions to his retrograde menstruation theory as well as important insights concerning endometriosis of the bowel [139]. Another important detail Sampson mentioned in his 1921 article was his belief that hemorrhagic ovarian cysts were in fact the same disorder as endometriosis, a conclusion he based on exhaustive microscopic analyses. As mentioned before, this was a crucial insight in the story of endometriosis, because it correlated with the same conclusion made by the nineteenth-century French group who suspected hemorrhagic ovarian cysts to be the same as catamenial hematoceles. In this way, albeit somewhat indirectly, the historical linkages between catamenial hematoceles and endometriosis can again be discerned.

However, Sampson's article from 1927, in which the term "endometriosis" was first proposed, proved to be one of the most influential publications in the history of endometriosis. It was in this work that Sampson introduced his retrograde menstruation theory (or we might say his reintroduction of Schrön's and Ruysch's reflux theories from more than two centuries before) as his working hypothesis to explain the presence of "heterotopic or misplaced endometrial tissue" [140]. Sampson also reported on his continued efforts to search for miscategorized diseases that might be endometriosis. With his microscope serving as the final arbiter, Sampson continued to uncover even more diseases that were microscopically confirmed to be endometriosis. Sampson's many distinct surgical philosophies were also evident in this and other articles. In contrast to Cullen, for instance, Sampson advised against surgical intervention for bowel lesions, suggesting instead total hysterectomy with bilateral salpingo-oophorectomy [141].

After Sampson Though the amount of research conducted before Sampson was not insubstantial, it was nothing compared with the thousands of articles written after Sampson's pivotal research reached the international airwaves. The much-needed consensus in taxonomy had finally been achieved, and eventually it was clear that the term "endometriosis" had been accepted into the fold of taxonomic convention. Within 20 years of Sampson's 1927 publications, endometriosis was found throughout the body and in teenage girls as well. Moreover, at least six theories of pathogenesis were advanced. Meanwhile, in 1925, the French gynecologist Cotte performed the first presacral nerve resection, a procedure that would one day be offered to endometriosis patients.

Before the end of the 1920s, reports of postoperative iatrogenic deposits in laparotomy scars had been reported [142], and important debates were under way about managing endometriosis as conservatively as possible. For example, in 1929, Lawrence R. Wharton published a seminal report about the use of conservative surgery for the removal of endometriotic lesions. Although others had suggested similar approaches, Wharton's work was especially influential given its arrival when

the heady days of multiple laparotomies were in full throttle. Atypical experiences continued to be noted as well, with studies demonstrating that even patients as old as age 85 could present with symptoms that required surgical intervention. The mystery of pathogenesis also continued to be a topic of great interest, and Halban conducted some of the best research on the subject [143].

The 1930s–1940s

By the end of the 1930s, endometriosis of the lungs, large bowel, colon, rectum, bladder, lymph nodes, cervix, and round ligaments had been reported [144–148]. More cases in teenagers were discovered, which launched a brief period of active research on the subject [149]. An article published in 1946 by Fallon was especially influential and brought this segment of the population into sharp relief [150].

Naturally, speculation about the etiology of endometriosis continued, with some reporting that endometriosis was probably of tubal origin, while others reevaluated the theories of the late nineteenth century [151]. Some reports were beginning to emerge that suggested endometriosis was not as rare as had been believed. Animal studies with endometriosis implants were also in progress [152, 153].

Twelfth-century androgenic treatments revisited Early in the decade of the 1940s, important advances in endocrinology were made by Fuller Albright, the father of modern endocrinology, which had far-reaching, positive consequences for endometriosis research. For example, testosterone and progesterone, first isolated and synthesized in the 1930s, had by now entered into the repertoire of therapies for endometriosis. The first English language article on the subject was published in 1941 by Geist and Salmon, who suggested using androgens as a potential treatment for endometriosis [122]. Of course, this was not the first time in history that prescriptions for hormone-disrupting substances were suggested for gynecologic disorders; recall that the Hippocratics had prescribed bull urine, and practitioners from the early twelfth century had suggested ground-up goat testicles as a treatment option.

Clinical trials The 1940s represented an era when endometriosis research clearly intensified. By the end of the decade, dozens of surveys and clinical trials had been published, with Keene and Kimbrough, Counseller, Payne, Fallas and Rosenblum, Holmes, Hayden, Sanders, Fallon, and Meigs cited as among the most notable investigators.

Understanding of the different types of lesions had also considerably advanced, which in turn led to the introduction of more nuanced surgical approaches. Some of the most important refinements in surgical techniques included the renewed interest in conservative approaches, particularly directed toward avoiding the removal of ovaries, a subject, which like today, was the focus of many heated debates. Meanwhile, after being effectively abandoned for nearly two decades,

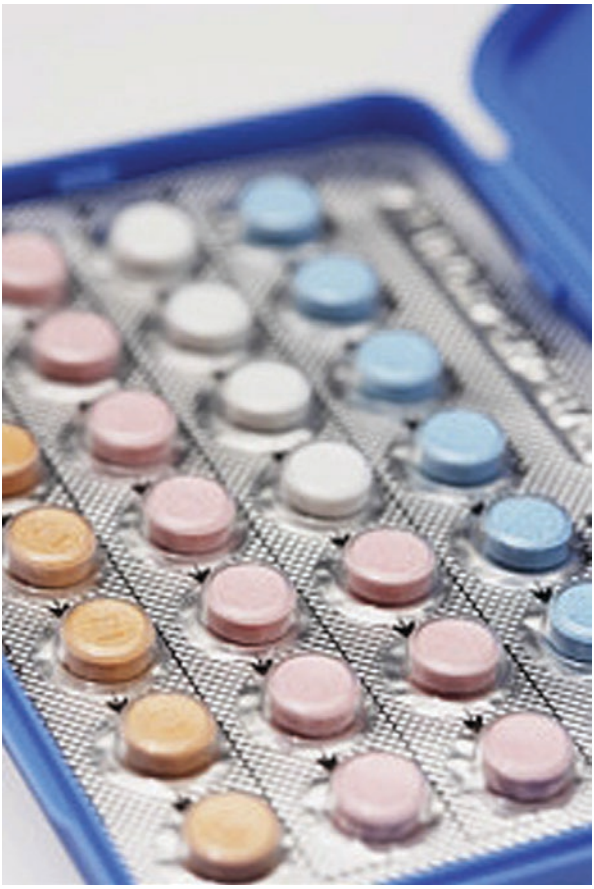


Fig. 2.59 One of the most pivotal breakthroughs in reproductive medicine was achieved by legendary pioneer, John Rock, in association with George Pinkus, who developed a hormonal contraceptive, first introduced in 1957. Among the first to be treated with this early version of the pill were women with endometriosis. (Reproduced with permission of Getty Images, photography by Lew Robertson.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

interest in laparoscopy began to reemerge as a viable diagnostic modality. Many attribute this change to the influence of legendary French gynecologist Raoul Palmer, whose innovations made the technique considerably safer and more reliable (Fig. 2.59).

Misdiagnoses and misconceptions As encouraging as this precipitous uptick in endometriosis research was, it did not completely curtail the vast array of spectacular misconceptions about women and pelvic pain that lingered in the popular imagination, some of which had been circulating since at least the late Iron Age. For instance, in a throwback to antiquity, twentieth-century physicians began urging women to get married and have children as soon as possible, the result of growing awareness about endometriosis' potential impact on fertility. Suggestions that endometriosis only afflicted certain social classes also continued to be made; one investigator from 1949 asked, "Is endometriosis principally a disease of the higher social and economic levels of society?" And, despite the groundswell of interest that Sampson had so decisively launched, many articles lamented the fact that endometriosis continued to be misdiagnosed.

The 1950s–1970s

The 1950s was a decade characterized by both controversial and pivotal developments. Routine pelvic exams became much more common in the United States as a result of growing awareness about cervical cancer in the wake of Papanicalau's research and his development of the Pap smear as an effective predictive technology. Driven by concerns about cervical cancer, surgical standards were also transforming: by the 1950s, the preferred form of hysterectomy in the United States had changed from supracervical to total abdominal hysterectomy.

It was during this time as well that one of the most pivotal breakthroughs in reproductive medicine was achieved by the legendary John Rock, who in association with George Pinkus developed a hormonal contraceptive, initially introduced in 1957 for the treatment of menstrual disorders. Among the first to be treated with this early version of the pill were women with endometriosis [154] (Fig. 2.60). However, given the limited understanding at the time about the pill's long-term effects, the initial prototypes were composed of such high doses of estrogen that many patients suffered considerable side effects. Some studies have suggested that higher incidences of cancers and other fatal complications later ensued among this early treatment population. Other promising new medical interventions were also introduced during this period, including Danazol, which arrived in the late 1970s via research by Greenblatt and Dmowski.

Even with this groundswell of novel treatment options, the overwhelming majority of studies indicated that endometriosis continued to be substantially misdiagnosed, with some reports suggesting that as many as 70% of cases during the 1970s went undetected [155]. These diagnostic delays were disappointing, but advances in research progressed at a rapid clip. Research into the theories of pathogenesis continued throughout this period, with Ferguson publishing some of the most important works in this area in 1969 [156]. Donald Chatman overturned long-standing myths concerning endometriosis, pelvic pain, and peritoneal pockets when he became one

Fig. 2.60 Raoul Palmer, pioneer of gynecologic laparoscopy. (Reproduced with permission of Journal of Society of Laparoendoscopic Surgeons, 1997;1[30]:289–92.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

of the first to demonstrate that as many as 68% of peritoneal pockets were infiltrated with endometriosis, a figure that jumped to 79% just a few years later after he had conducted even larger studies.

In terms of surgical options for women with endometriosis, multiple laparotomies and hysterectomies remained the standard surgical interventions of the day. However, laparoscopy continued to demonstrate its diagnostic prowess, the first step toward ending the practice of relying on exploratory laparotomies as a diagnostic modality. By 1955, Palmer had made headlines with his debut of the first color film of a live laparoscopy; a few years later, Hans Frangenheim of Germany would produce his famous 1958 color film of a laparoscopically captured ovulation in progress, a feat that would reverberate throughout the world of gynecologic laparoscopists for years to come [157]. By the end of the 1960s, Melvin Cohen and Alvin Siegler were treating tubal disease laparoscopically, one of the first truly minimally invasive surgical options of the twentieth century to have been offered to patients with endometriosis of the tubes.

Throughout the 1970s, Batt, Brosens, Bruhat, Buttram, Clarke, Darai, DeCherney, Franklin, Gomel, Hasson, Levinson, Manhes, Rioux, Rock, and many others achieved similarly significant advances in microsurgical techniques and other minimally invasive methods. Gomel, for example, reported improved fertility outcomes after applying his meticulous microsurgical techniques [158, 159]. Other surgical advances involved new technologies or techniques, such as bipolar devices that were developed and adapted for use with laparoscopic surgery in 1973 by five independent sources: Cloutier, Corson, Hirsh, Kleppinger, and Rioux [160–162]. Hasson's 1971 introduction of "open laparoscopy" allowed for direct visualization during trocar placement [163]. Clarke's laparoscopic suturing innovations were especially crucial for enabling progress toward operative laparoscopy [164, 165]. Meanwhile, in 1979, the team of Bruhat, Mage, and Manhes, became one of the first to apply a CO_2 laser in laparoscopic procedures, while Yona Tadir of Israel independently accomplished the same a few months later [166]. Bellina, Donnez, Diamond, Martin, Sutton, and Tulandi were also among the earliest to incorporate the laser into their gynecologic surgery practices. By 1974, Kurt Semm had expanded laparoscopy into therapeutics, achieving some success in treating mild to moderate disease [167, 168].

However, in these pre-video days, the awkward manner in which laparoscopy was performed—bending over and squinting with one eye closed into the scope's tiny aperture—limited its operative utility to only the simplest procedures. Even then, only the era's few virtuosos—Bruhat, Cohen, Frangenheim, Gomel, Manhes, Palmer, Semm, and Steptoe—could perform laparoscopy in its cumbersome premodern form. For the vast majority of surgeons, pre-video operative laparoscopy was infeasible and ineffective. For the vast majority of women with endometriosis; even those with mild cases but especially those with severe, multiorgan disease, it was almost as though nothing had changed: The inescapable reality was that multiple laparotomies and hysterectomies remained the only viable surgical choices until the introduction of videolaparoscopic surgery in the late 1970s.

Treatment Options: The 1900s–1970s

As mentioned, the period between 1900 and 1970 was characterized by unprecedented advances in medicine. It was a time when bacteria took a backseat to penicillin, and when the average life span in the developed world nearly doubled. Yet when it came to the treatment of endometriosis, only five effective therapeutic options were offered in this same 80-year time frame:

1. Subtotal and/or total hysterectomy, with bilateral salpingo-oophorectomy
2. Hysterectomy with conservation of ovaries
3. Conservative approaches, such as excisional techniques
4. Treatment with radium
5. Hormone treatments

Within these categories, many nuances continued to be debated. For example, there continued to be deliberations about whether to preserve the ovaries. Meanwhile, although Cullen used radium on the rectum for any pathology that was left after surgery, radiation therapy was thankfully abandoned by about the early 1950s. Discussions also continued about whether vaginal or abdominal hysterectomies were best. By the mid-twentieth century, abdominal hysterectomies had clearly prevailed in Germany, Britain, and the United States, but the vaginal route continued to be favored in France.

By the 1950s, some women were already undergoing multiple laparotomies for endometriosis. In the early half of the twentieth century, patients undergoing abdominal surgeries could expect to receive enemas of turpentine, boiled brains for lunch, alcohol and strychnine for any postoperative cardiac events, arsenic for anemia, and mortality rates of between 5% and 10% [100, 169] (Fig. 2.61). By the mid-1950s, after the introduction of improved anesthetics, blood transfusions, and intravenous therapies, mortality had dropped to about 25 in 1000 [169].

Video-Assisted Laparoscopic Surgery "V.A.L.S."

In the late 1970s, Camran Nezhat introduced video-assisted laparoscopy. Prior to this, even mild cases of endometriosis Camran were being treated by laparotomy. By 1984–1986, Nezhat reported successful treatment of extensive endometriosis, which proved that it was possible to treat even the most extensive endometriosis by laparoscopy [170, 171] (Figs. 2.62 and 2.63). Within a few years, at the 44th annual meeting of the American Fertility Society in October of 1988, the first successful laparoscopic treatment of endometriosis of the bowel was reported by Nezhat [172]. Another milestone was achieved when Nezhat became the first to report on laparoscopic radical hysterectomy, with paraaortic and pelvic node dissection [173, 174]. The first laparoscopic hysterectomy reported by Reich in 1989 was another highlight of the late 1980s [175]. In subsequent years, the Nezhats reported on the

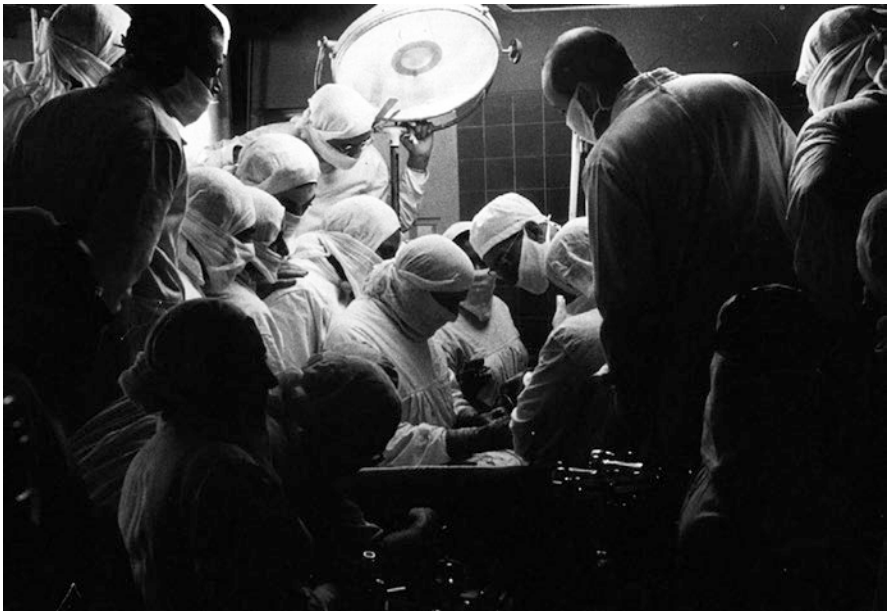


Fig. 2.61 Operating room from about the mid-twentieth century. (Reproduced courtesy of the U.S. National Library of Medicine and the World Health Organization, Call No. PPO44534, WHO, box 1.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

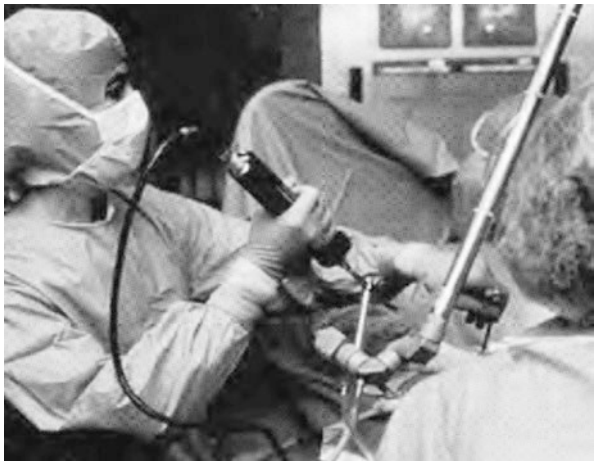


Fig. 2.62 Camran Nezhat, circa 1980, performing videolaparoscopy with one of the early video camera prototypes. *Nezhat. Endometriosis in history. Fertil Steril 2012*

successful laparoscopic treatment of the most complicated benign and malignant pathologies, including endometriosis of the bladder, ureter, diaphragm, liver, and lung. Important new advances in minimally invasive treatment options for endometriomas were also introduced by the Nezhats [176–185].

Fig. 2.63 Image from 1977 showing how laparoscopy used to be performed, bending over and squinting with one eye closed to peer through the small aperture. (Reproduced with permission of the Royal Society. Proceedings B, 1977;195[1119].). *Nezhat. Endometriosis in history. Fertil Steril 2012*

The introduction of video-assisted endoscopy by Nezhat, together with his foresight to treat even the most advanced pathologies endoscopically, revolutionized modern-day surgery and transformed minimally invasive surgery into a truly viable discipline that will eventually replace almost all forms of open surgery. The increasing application of advanced operative laparoscopy is a direct consequence of the surgical ingenuity of the early pioneers [172, 186–188]. Multiple studies have established that laparoscopy results in lower morbidity, better visualization of areas difficult to access thus allowing for more precise dissection, decreased blood loss, decreased postoperative pain, and faster recovery [176]. Over time, the extent of laparoscopic dissection expanded. After the outcomes of video-assisted endoscopy consistently proved superior to open surgery, it was clear that even the most extensive pathology could be managed endoscopically. Therefore, since the 1980s, our facility has been performing and advocating for a minimally invasive approach for almost all surgical procedures [189, 190]. As we have reported over the years, essentially the only limiting factors of video-assisted endoscopy are the skill and experience of the surgeon and the availability of proper instrumentation [171, 179]. Initially, our declaration that almost all laparotomies can be avoided was not popularly received. It was not until 2004 that the *New England Journal of Medicine* recommended and encouraged the same advanced methods and techniques for the same exact procedures that we were the first to introduce nearly two decades earlier. Ironically, too, these same procedures now recommended over open methods are the same ones that were being called "barbaric" just a few years ago [172, 191].

In a strange way, it may be endometriosis that we have to partially credit for shaping the course of surgery away from large incisions and toward video-assisted laparoscopy. After all, if bowel resections and debulking of extensive and infiltrative pelvic endometriosis, some of surgery's most difficult procedures, could be accomplished laparoscopically, this meant that practically any other procedure also could be performed by this technique, providing the same significant benefits to patients.

Endometriosis has influenced surgical history in other surprising, even counterintuitive ways. For example, even though women had been undergoing abdominal surgeries at least since McDowell's debut surgery of 1809 [192, 193], it is curious to note that the multitude of morphologies that endometriosis can take was not fully recognized until late in the twentieth century. For example, even though Cullen,

Sampson, and others had reported on extragenital endometriosis in the early 1920s [126, 194], many years went by before researchers realized it could also infiltrate arteries, blood vessels, bone, brain, and the diaphragm. The anguish of preteen and teenage girls with endometriosis also was nearly completely overlooked for most of the twentieth century because it had been assumed that this age group was only rarely if ever afflicted. As modern research now demonstrates, the disease has been found in patients as young as 8 years to as old as 91 years, as was first reported by Babes in 1882 [100, 107, 195, 196].

As for its prevalence in teenagers, a recent study by Opoku-Anane and Laufer found that as many as 98% of teenagers who report chronic pelvic pain that is unresponsive to conventional therapy have endometriosis.

Because of lingering beliefs associating pelvic pain with promiscuity, women continued to be blamed for their illnesses. Women from US minority communities have been especially susceptible to being misdiagnosed with diseases that imply sexual transgression. Don Chatman was the first to scientifically debunk these views in 1976 with his seminal article "Endometriosis in the Black Woman," in which he reported that as many as 21% of African American women with pathology-confirmed endometriosis had been mistakenly diagnosed with pelvic inflammatory disease (PID) [197]. Yet nearly 20 years later, dismal statistics were still being reported: one study from 1993 found that "as many as 40 percent of African American women [were] misdiagnosed as having a sexually transmitted PID when in fact they [suffered] from endometriosis" [198]. The study did not provide the corresponding rates of misdiagnoses that occurred in other groups, which makes it difficult to make comparisons between different populations, but it is clear that en masse misdiagnoses of women with endometriosis have been the norm.

However, of all the misconceptions about endometriosis, it is arguably the centuries-old notion linking pelvic pain to mental illness that seems to have been most responsible for causing diagnostic delays and chronic indifference to women's complaints of pain. Indeed, for most of the twentieth century, women experiencing pain without any perceptible organic cause were often assumed to be hysterical or mentally unstable. With such mass misdiagnoses pervading the landscape of women's medicine, until recently many patients with endometriosis were just as likely to be sent to a psychiatrist as a gynecologist when their inexplicable, multiorgan symptoms were mistaken for psychosomatic disorders instead [199]. In short, despite its presumably ancient presence among us, endometriosis continued to evade the clinical gaze, eluding all attempts to understand its enigmatic essence, even after the large incisions of laparotomies should have helped surgeons detect its presence.

When surgeons converted to video-assisted laparoscopy, they gained a completely new understanding of the anatomy. For the first time, too, surgeons were able to consistently visualize atypical lesions that before might have easily been mistaken for normal tissue but under magnification could clearly be seen as pathological formations. Such stunning visualization had never been obtained while performing diagnostic laparoscopies by the old method of peering into an eyepiece, or even from the vantage point of the supposedly superior view afforded by large laparotomy incisions [200] (Figs. 2.64 and 2.65). Using the new technique allowed for visualization of lesions as small as 400 mm for red and 150 mm for clear lesions [129].

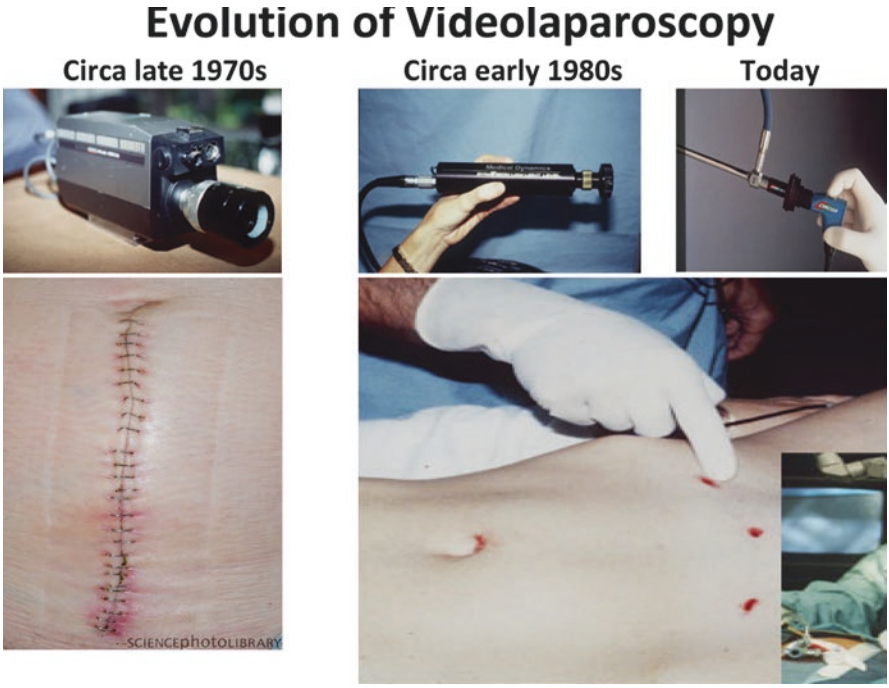


Fig. 2.64 The evolution of videolaparoscopy cameras and incisions. (Images of cameras and videolaparoscopy scars courtesy of Dr. Camran Nezhat. Image of laparotomy scar reproduced with permission of Dreamstime.com and photographer Rasumrok1, image no. 15610695.). *Nezhat. Endometriosis in history. Fertil Steril 2012*

With an improved ability to visualize pathologies that had gone undetected for centuries, video-assisted endoscopy contributed to an era of greater understanding about the true nature of endometriosis, anatomy, and other disorders, finally uncovering what patients had been suffering from all along [129, 201]. By the late 1980s, newly converted video laparoscopists began to report similar clinical findings, overturning nearly a century of statistics that had misrepresented the true prevalence and severity rates of endometriosis [129, 202]. As one report from 2011 concluded, many now believe that with "the enhanced magnification available with modern-day laparoscopy, virtually all endometriosis can be identified."

Surgical Progress: The 1980s–1990s

After the excellent results of video-assisted laparoscopy became apparent, more moments of envelope-pushing were made by such pioneers as Abrao, Adamyan, Adamson, Brosens, Canis, D'Hooghe, Donnez, Dubuisson, Falcone, Fazleabas, Fusi, Griffith, Hunt, Koninckx, Koh, Lee, Luciano, Mage, Malinak, Martin, Matzoni, Mencaglia, Miller, Minnelli, Nisolle, Olive, Perry, Possover, Pouly,

Fig. 2.65 Nezhat holding one of the first video cameras he used when he first introduced videolaparoscopy. *Nezhat. Endometriosis in history. Fertil Steril 2012*

Redwine, Reich Ussia, Vercillini, Vilos, Wattiez, and Zupi, to name but a few, all of whom had achieved crucial milestones and made substantial refinements in surgical techniques and technologies [186, 188].

New technologies developed specifically for video-assisted endoscopy were also finally becoming available, allowing surgeons to branch out even further in the minimally invasive direction. Novel laparoscopic techniques such as single-port laparoscopy, introduced by M. A. Pelosi, were developed, as well as robotic technologies such as Intuitive Surgical's da Vinci robot, developed by a team led by Ajit Shah and Phil Greene of Stanford Research International.

Other Achievements: The 1980s–Present

Throughout the 1980s and to the present time, breakthroughs in basic science research have continued [203]. Russell and Jansen were the first to report on non-pigmented lesions in 1986, with Koninckx, Martin, and Redwine independently reporting similar findings soon after. Although the CA-125 glycoprotein was initially introduced by Bast in 1983 as a serum marker for epithelial cancer of the

ovary, within a few years, Barbieri would publish his landmark 1987 study on its role as a potential biomarker for endometriosis. Koninckx and Martin were also early investigators of CA-125 and reported important new findings. Meanwhile, Redwine and the team of Koninckx and Martin separately reported ground-breaking new research on deep infiltrative endometriosis (DIE). Their reports led to a sea change of new awareness about DIE, which had been particularly poorly understood and commonly overlooked. The 1980s also marked a time when extensive research on the gonadotropin releasing hormone (GnRH) agonists and prostaglandin inhibitors was underway. By 1997, Hornung et al. [204] achieved progress in understanding how immunologic dysfunction might play a role in the development of endometriosis. Linda Giudice of the University of California at San Francisco has achieved tremendous insights into the genetic and molecular pathways involved in the development of endometriosis.

Many organizational innovations also have been made, including the founding of the Endometriosis Association in 1980 by co-founders Mary Lou Ballweg and Carolyn Keith, the Endometriosis.org in 2005 by Lone Hummelshoj, and the Endometriosis Foundation of America in 2009 by co-founders Padma Lakshmi and Dr. Tamer Seckin. Many world congresses on endometriosis are now being held, but the first one was The World Congress on Endometriosis, held in Clermont-Ferrand, France, in 1986.

More data on the genetic pathways of endometriosis also have been reported. A study headed by Hugh Taylor of Yale Medical School found a mutation in part of the *KRAS* gene that is associated with abnormal endometrial cell growth and decreased progesterone receptor levels. Compared with the general population where only 5% are estimated to have this mutation, in their study group of 150 women with endometriosis, 31 were found to carry a variant allele of the gene which altered its binding with let-7 microRNA [205]. Another intriguing new report suggests that viable stem cells present in menstrual blood may be triggering the development of endometriosis; if true, this would give new credence to the retrograde menstruation theory of pathogenesis and would also help explain how and why endometriosis can recur despite multiple surgeries. Advances in the understanding and treatment of endometriosis-associated ovarian carcinoma have also been highlighted in recent decades [206, 207].

Final Thoughts

In looking back at how far we have come, it is heartening to see that such extraordinary progress has been made. However, as one practitioner remarked in 2004, we are still in a state of "aetiological confusion and therapeutic anarchy" when it comes to the study and treatment of endometriosis [208, 209]. Not surprisingly, many questions remain unanswered, but what we can say with reasonable assurance is that endometriosis appears to be an old disease that has affected women for millennia. Allusions to its insidious presence are documented in ancient medical texts

dating back more than 4000 years. That endometriosis appears to have such an ancient lineage makes it all the more surprising that it is, for the most part, still an enigma. Perhaps most remarkably, some treatments have remained the same for hundreds of years with only minor variations.

Our research also revealed that the theories used to conceptualize women's illnesses throughout the ages were highly susceptible to the influences of culturally determined notions of illness. This was a timely reminder that medical beliefs are never just the products of objective science but are equally likely to be reflections of the shifting whims of social norms. We also can see that, on some level, pelvic pain has been believed for centuries to be the deserved consequence of presumed depravity on the woman's part—their imagined madness, weakness, or promiscuity manifesting as otherwise inexplicable cases of chronic pelvic pain.

As for the centuries-long, unsolved mystery of hysteria, we believe that enough credible evidence exists to substantiate our hypothesis that hysteria was most likely endometriosis in the majority of cases. Even though hysteria was largely discredited in modern times, nevertheless it continued to exert tremendous influence on attitudes about women and illness for most of the twentieth century.

Sadly, this painful legacy of diagnostic disarray continues. Even today, many women with endometriosis report that they are told "it's all in their heads," a throwback to the hysterical concept. And, with reports from as recently as 1995 finding that, on average, over 50% of women with chronic pelvic pain were found to have no "organic" basis—this meant that essentially half of all women who sought medical care for pelvic pain remained medical castaways, with some still considered hysterical or mentally unstable [199]. Such diagnostic oversights have been most likely contributing to the rarely discussed phenomenon of unnecessary, "nontherapeutic" appendectomies: according to some studies, as many as 52% of all emergency appendectomies performed in women turn out to be unwarranted [210–216]. As a consequence of these centuries-old misconceptions, women today still face considerable challenges in securing a diagnosis: on average, 6 to 7 years pass before a woman is correctly identified as having endometriosis [155]. And, perhaps most surprisingly, we continue to recommend pregnancy as a form of treatment, the same prescription offered over 4000 years ago.

In terms of technologic challenges, there have been many breakthroughs, but we are still years away from introducing an accurate, noninvasive diagnostic test. Meanwhile, the majority of hysterectomies for endometriosis are still being performed abdominally instead of with minimally invasive methods. Despite nationwide training efforts, only a small fraction of surgeons can perform some of the more advanced laparoscopic techniques, leaving the choice of laparotomy as the default response.

Lessons learned As for the lessons learned from this retrospective review spanning over 4000 years, the repeated observations made in Greco-Roman medical traditions especially have provided us with a greater appreciation of the potentially significant affects endometriosis can have on teenagers. Perhaps we should be refocusing our efforts on earlier clinical screenings and intervention for this

population. Intervening at this early age could potentially reduce damage to organs and possibly even induce a remission.

We also discerned patterns of social practices that potentially offer insight into both historical and modern epidemiologic trends. For example, the fact that the Hippocratics were advising that changes in marriage practices be made partially in response to an endometriosis-like illness would seem to indicate that the disorder was believed to be fairly widespread. Since their inferences about prevalence rates were drawn from a comparatively small population pool, this in turn would suggest that the Hippocratics may have had rates that were somewhat higher than the 5–15% range commonly cited today. Other epidemiological inferences can also be made based on these historical findings. For example, if the Hippocratics were indeed encountering endometriosis enough to view it as a fairly common disorder, we might need to re-think contemporary theories which implicate dioxins, PCBs, and other modern chemicals as causative agents.

Still, despite the lingering challenges and ambiguities, it is clear that we have achieved appreciable progress. Instead of enduring excruciating pain or multiple laparotomies, women now have promising medical treatments as well as minimally invasive surgical options that can treat the disorder while preserving fertility. And, finally, patients at least now have a chance to be properly diagnosed, freeing them from thousands of years of misdiagnoses, when their menstrual pain was presumed to be an inescapable, biological destiny.

An integrated theory of pathogenesis: multiple perspectives As for the "etiologic chaos" that persists, drawing from over 30 years of endometriosis research and surgical experience, which includes by now approximately 14,000 surgeries, several important insights come to mind. The first is that we believe it is time to radically reevaluate the conceptualization of the four main theories of pathogenesis. In our view, all four theories are partially correct. We arrived at this hybrid theory after observing what we suspect to have been all four pathogeneses at play: (1) retrograde menstrual endometrium implanting on peritoneal surfaces and transforming into pathology; (2) a pattern of coelomic metaplastic differentiation of mesothelial cells into endometrium-like tissue; (3) lymphatic and venous spread transporting and depositing endometriosis into areas that cannot be explained by the other theories; and (4) iatrogenic or direct transplantation, which would explain the presence of endometriosis in surgical scars. Rather than viewing these theories from a zero-sum standpoint, we believe that conceptualizing endometriosis through the framework of an integrated model could potentially lead to significant improvements in preventive and treatment strategies, as well as potentially lead us closer to a cure.

Another important insight that we have gained concerns prevalence rates. Over the years, our views on this subject have changed dramatically after repeatedly noting that a strong relationship between endometriosis and leiomyomata seems to exist. Fibroids arise from a single precursor via monoclonal proliferation. A similar mechanism should be considered and investigated for endometriosis. In fact, if we consider endometriosis and leiomyomas to be of the same spectrum of disease, the

missing link is adenomyosis. After all, adenomyosis is essentially endometriosis of the uterine muscle, and an adenomyoma is essentially a tumor of endometriosis of the uterine muscle.

In one of our recent studies, we looked at 131 women undergoing surgical intervention for symptomatic leiomyomas and found that 113 had pathology-confirmed endometriosis, representing an 86% correlation between the two entities [217]. Extrapolating from these findings, we then considered the prevalence rates of fibroids. It has been well established that fibroids have a prevalence of 30–50% [218]. With a world population of approximately 3.5 billion women, that means an estimated 1.05–1.75 billion women either have had, will have, or currently do have fibroids. Given our hypothesis that at least an 86% coexistence of endometriosis and fibroids exists, that would suggest that there are 900 million to 1.5 billion women who also either have had, will have, or currently do have endometriosis. This is a far higher estimate than the 5–15% prevalence generally cited for endometriosis [219]. Physicians have long known that endometriosis is underdiagnosed, but our hypothesis suggests that the incidence in which endometriosis is overlooked is substantially higher than previously thought.

If we begin to solve the enigma of endometriosis and fibroids, we may also be able to open the door to understanding, curing, and preventing reproductive cancers. Every female is born with the potential for both fibroids and endometriosis. A trigger or stimulus which has yet to be fully identified then leads to either the development of fibroids and endometriosis or their suppression by hitherto unidentified protective mechanisms. That trigger may even be found in utero. A 2012 study analyzed 52 female fetuses at autopsy and found endometriosis in four of the fetuses studied [219]. To date, however, no studies have looked at the prevalence of adenomyosis, adenomyoma, and leiomyomas in fetuses.

Endometriosis: one name, many diseases Considering the extraordinary range of morphologies and endlessly disparate reactions endometriosis expresses in response to both surgical and medical interventions, perhaps we are asking the wrong questions. Just as we define cancers today in the plural, we may soon come to recognize endometriosis in the same way: a disorder with multiple phenotypes that share similar molecular mechanisms and reside on the same spectrum, but which manifest differently in each individual as a result of unique environmental, genetic, or epigenetic triggers: endometriosis, adenomyosis, adenomyomas, leiomyomas … with the potential to progress to endometrioid adenocarcinoma. Although the true workings of these biologic mechanisms currently remain under lock and key, what we do know for certain is that more research is needed to uncover the origin of endometriosis. Again, we believe the answer will be closely linked to the origin of fibroids. Another possible research direction that has yet to be explored relates to the fact that the spleen appears to contain a protective environment that prohibits the growth of endometriosis. Discovering what those precise protective mechanisms are could also help lead us to a cure.

All our observations highlight the fact that we need to continually drive forward our efforts to provide better training opportunities for physicians so that

endometriosis can be properly diagnosed and treated. This is the only way that we can unravel the enigma of endometriosis and end its devastating reign over so many lives. The clock is definitely ticking as we know that millions of women still live lives awash in anguish, just as they did thousands of years ago, and just as they will centuries from now unless we can steer ourselves faster toward the long elusive cure. Four thousand years is long enough; the time has come to end the empire of endometriosis.

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Chapter 3
Endometriosis in Adolescents

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Introduction

Endometriosis, defined as endometrial tissue implanted outside the uterus, has been estimated to affect 10% to 15% of all reproductive-age women [1] and 70% of women with chronic pelvic pain [2]. Less established are the rates of laparoscopically confirmed endometriosis among adolescent females with pelvic pain; these estimates range from 19% to 73% [3–5]. One prospective study estimated the prevalence of endometriosis among adolescents with pelvic pain who underwent laparoscopy at 47% [6], and two retrospective studies found endometriosis in 70% to 73% of adolescents with pelvic pain that was unresponsive to medical therapy [7, 8].

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Although most women with endometriosis report the onset of symptoms during adolescence, diagnosis is often delayed [9]. Consequently, this delay may decrease their reproductive potential and functional outcomes. Moreover, early identification and treatment of endometriosis may resolve pain, prevent disease progression and organ damage, and preserve fertility [10].

Adolescents with pelvic pain may present a diagnostic challenge, because they describe acyclic pain as well as cyclic pain and may present with an array of confounding symptoms [9]. The intraoperative appearance of endometriosis in adolescents may differ from the classic "powder-burn" lesions typically seen in adults [11]. Furthermore, the healthcare costs associated with adolescent endometriosis are significant, not to mention the social and emotional costs to the girls caused by absenteeism at school and inability to participate in normal activities [12].

In this study, we describe the experience of adolescent females with severe pelvic pain that was refractory to medical management, who underwent laparoscopy, during which endometriosis was ultimately diagnosed. We characterize the constellation of symptoms that led to incorrect diagnoses, time from onset of symptoms to diagnosis, type and number of different medical professionals seen before diagnosis, prevalence of endometriosis in the population, surgical findings, and postoperative outcomes at 1 year.

Materials and Methods

Study Design

This retrospective case series included consecutive adolescent females with pelvic pain who underwent laparoscopy and received a visual and histologic diagnosis of endometriosis at our tertiary surgical referral center between January 1, 2001, and December 31, 2009. Inclusion criteria were age 21 years or younger, pelvic pain refractory to medical management, and a history of multipuncture laparoscopy for pelvic pain. Exclusion criteria were previous surgical diagnosis of endometriosis and preoperative radiographic evidence of endometriosis (i.e., endometriomas). Those two populations were excluded because we wanted to establish the prevalence of endometriosis in adolescents without historical or radiographic evidence of disease. Figure 3.1 describes the selection process for the study.

Preoperative demographic and clinical data were obtained from the patients' medical records. Demographic data included age, body mass index (BMI), and race. Clinical data included gravidity, parity, age at menarche, coital status, family history of endometriosis (defined as a first- or second-degree relative with diagnosed endometriosis), and preoperative patient symptoms. Information regarding referral sources to our tertiary care center, time from the onset of symptoms until diagnosis of endometriosis, time from menarche until diagnosis, time from the first physician visit until diagnosis, number and specialties of physicians seen, prior diagnoses,

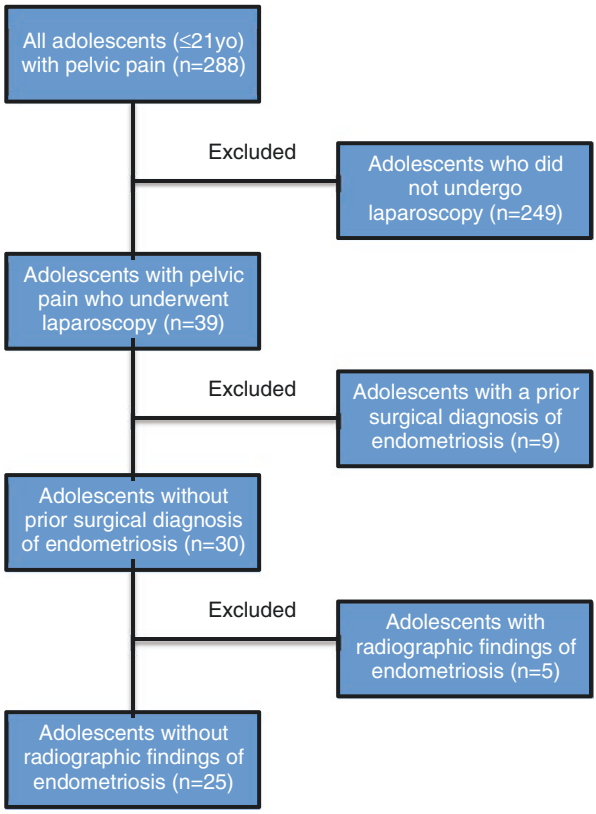

Fig. 3.1 The selection process for the study

prior trials of medical therapy, and prior surgery were also obtained from the patients' medical records. The detailed information about severity and duration of symptoms and previous diagnoses and treatments were obtained in a standard history obtained during the first office visit.

All patients who underwent laparoscopy had a preoperative diagnosis of severe pelvic pain that was refractory to medical treatment. They underwent multipuncture laparoscopy as previously described [13]. One surgeon (C.H.N.) performed all the procedures. Endometriosis was diagnosed by visual inspection and by histopathologic analysis of biopsy specimens. The surgical treatment consisted of a combination of excision and ablative techniques to achieve maximal removal of the lesions. The severity of disease was staged according to the revised American Fertility Society classification system [14]. Postoperative clinical information regarding postoperative medical treatment if any, subsequent abdominal and pelvic pain, subsequent surgeries for endometriosis or other etiologies, attempted pregnancies, and pregnancies were retrospectively obtained from the patients' medical records. Postoperative follow-up was assessed at 1 year. This study was ruled exempt by the Institutional Review Board at Northside Hospital (Atlanta, Georgia).

Statistical Analysis

Descriptive statistics was used to analyze the data. Results were reported as the mean (SD) and range of values or number (*n*) and percent (%) of the study group. Analyses were performed with the statistical software package SPSS 22.0 (IBM, Armonk, New York).

Results

Two hundred eighty-eight adolescent females with pelvic pain were initially identified. Two hundred forty-nine were excluded because laparoscopy was not performed, 39 underwent laparoscopy for pelvic pain, 9 were excluded because they had prior surgical diagnosis of endometriosis, and 5 were excluded because of radiographic evidence of disease (i.e., endometriomas). Twenty-five patients met the inclusion and exclusion criteria and were analyzed in this case series. Figure 3.1 traces the selection process. The mean age at the time of surgery was 17.2 (2.4) years (range, 10–21). Fifty-six percent had a family history of endometriosis. Other demographic and preoperative clinical characteristics of the patients are described in Table 3.1. The most common preoperative complaints (Table 3.2) were

Table 3.1 Patient demographics and clinical information

Variable	Data
Patients, *n*	25
Age at surgery, years	17.2 (2.4); 10–21
BMI, kg/m^2	23.0 (3.9); 19–35
Race, *n* (%)	
White	23 (92%)
Black	2 (8%)
Gravidity	0 (0.4); 0–2
Parity	0 (0.4); 0–2
Sexually active, *n* (%)	
Yes	8 (32%)
No	17 (68%)
Family history of endometriosis, (%)	
Yes	14 (56%)
No	11 (44%)
Age at menarche, years	12.2 (1.1); 10–14
Time from menarche until diagnosis, months	56.9 (31.4); 12–132
Duration of symptoms before diagnosis, months	22.8 (31.0); 1–132

BMI body mass index. Unless otherwise noted, data are presented as the mean (SD); range

Table 3.2 Preoperative subjective symptoms[a]

Symptom	*n* (%)
Dysmenorrhea	16 (64)
Menorrhagia	11 (44)
Abnormal/irregular uterine bleeding	15 (60)
Dyspareunia	4 (16)
Genitourinary symptoms	
Bladder pain	1 (4)
Flank pain	1 (4)
Back pain	6 (24)
Dysuria	4 (16)
Urinary frequency and urgency	9 (36)
Urinary incontinence	2 (8)
Hematuria	2 (8)
Nocturia	3 (12)
Gastrointestinal symptoms	
Nausea	11 (44)
Constipation	5 (20)
Diarrhea	6 (24)
Dyschezia	7 (28)
Hematochezia	3 (12)
Constitutional symptoms	
Fatigue	6 (24)
Acne	5 (20)
Headache	2 (8)
Insomnia	1 (4)
Premenstrual dysphoric disorder	6 (24)
Depression	1 (4)

[a]Patients may have had more than 1 symptom

dysmenorrhea (64%), menorrhagia (44%), abnormal or irregular uterine bleeding (60%), at least one gastrointestinal symptom (56%), and at least one genitourinary symptom (52%).

Table 3.3 describes the referral patterns and prior diagnoses. On average, the amount of time between the first physician visit for pelvic pain and diagnosis was 10.9 months (22.0) (range, 1–108). The median number of physicians from different specialties who evaluated the patients' pelvic pain was 3 (2.3) (range, 1–12) and included ≥1 obstetrician/gynecologists (72%), gastroenterologists (36%), urologists (16%), and other specialists, including orthopedic surgeons, infectious disease physicians, pain management specialists, physical therapists, and psychiatrists. Eleven of the 25 (44%) adolescents had been to the emergency department at least one time because of pelvic pain. The patients had diagnoses of other illnesses, including pelvic inflammatory disease (PID) (20%), irritable bowel syndrome (IBS) and gastritis (16%), ovarian cysts (12%), musculoskeletal pain (12%), and appendicitis (12%). The patients' mothers (44%) provided the primary referral to our

Table 3.3 Referral patterns and diagnoses

Variable	Data
Time from first physician visit until diagnosis, months	10.9 (22.0); 1–108
Median number of physicians seen before diagnosis	3 (2.3); 1–12
Type of physicians seen before diagnosis, *n* (%)[a]	
Obstetrician/gynecologist	18 (72)
Emergency room physician	11 (44)
Gastroenterologist	9 (36)
Urologist	4 (16)
Internal medicine physician	4 (16)
General surgeon	3 (12)
Pediatrician	3 (12)
None	3 (12)
Other	6 (24)
Prior diagnoses, *n* (%)[a]	
Endometriosis, not surgically diagnosed	5 (20)
Pelvic inflammatory disease	5 (20)
Irritable bowel syndrome/gastritis	4 (16)
Dysmenorrhea	4 (16)
Appendicitis	3 (12)
Ovarian cysts	3 (12)
Musculoskeletal pain	3 (12)
Renal colic/interstitial cystitis	2 (8)
Crohn's disease	2 (8)
None	4 (16)
Other	3 (12)
Average number of months on COCs (*n* = 17)	13.5 (20.6); 1–84
Average number of months on NSAIDs (*n* = 10)	7.5 (9.1); 1–24
History of prior surgery (*n* = 25), *n* (%)	
Yes	3 (12)
No	22 (88)
Referral source (*n* = 25), *n* (%)	
Mother	11 (44)
Obstetrician/gynecologist	6 (24)
Friend of the patient's family	4 (16)
Internal medicine physician	2 (8)
Emergency room physician	1 (4)
Nutritionist	1 (4)

[a]Patients may have had more than 1 doctor or diagnosis. Unless otherwise noted, data are presented as the mean (SD); range

tertiary care center, followed by another obstetrician/gynecologist (24%) and friends of the patients' family (16%).

In all 25 patients, endometriosis was diagnosed during the laparoscopy. Eighteen (72%) had biopsy-proven endometriosis, and seven (28%) had visual diagnosis of

endometriosis, but extensive biopsies were not performed because of the anatomic location of the endometriosis. Most of the patients in whom diagnosis was visual had fibrotic clear vesicular lesions and peritoneal defects. Most of the adolescents had stage I (68%) endometriosis, followed by stages II (20%) and III (12%), according to the Revised American Society for Reproductive Medicine classification of endometriosis [14]. None of the adolescents had stage IV endometriosis or evidence of extragenital endometriosis. The types of endometriosis lesions most commonly visualized were peritoneal defects (Fig. 3.2) and atypical white/ fibrotic (Fig. 3.3), clear (Fig. 3.4), ovarian or cortical (Fig. 3.5), hemosiderin/pigmented (Fig. 3.6), and hemorrhagic (Fig. 3.7). Table 3.4 describes the perioperative patient findings.

After the laparoscopy, most of the patients were given one or more medications, most commonly combined oral contraceptives (COCs) (64%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (32%). At 1 year, 64% reported resolved pain, 16% reported improved pain, 12% reported continued pain, and 8% stated that the pain had initially improved but then had returned. Table 3.5 summarizes the postoperative treatments and pain outcomes at 1 year.

Discussion

In a survey of more than 4000 women reporting surgically diagnosed endometriosis, two-thirds of the respondents experienced symptoms during adolescence. Those women were far more likely to be told by their physicians that nothing was wrong, as opposed those who sought treatment for symptoms that started later in life [9].

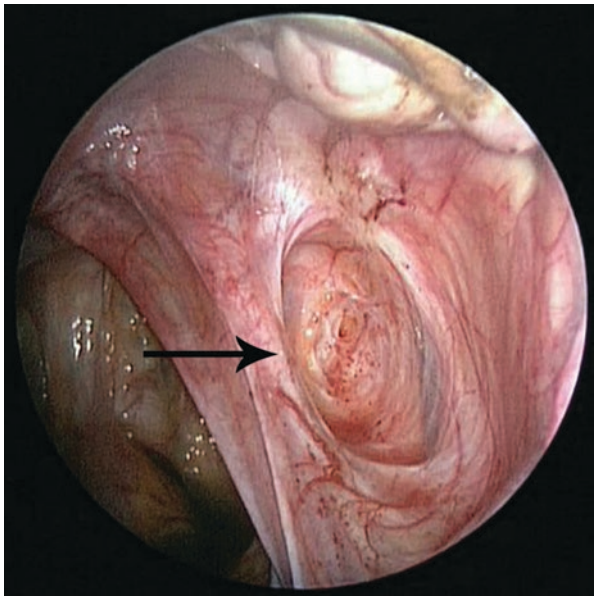

Fig. 3.2 Peritoneal defect (arrow) with red, punctate lesions in the center of the defect in the right ovarian fossa in a 16-year-old patient with stage II endometriosis

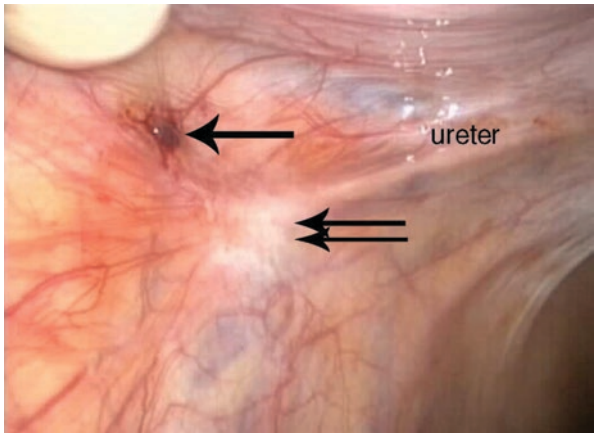

Fig. 3.3 Hemorrhagic endometriosis (arrow) involving the left pelvic sidewall with an atypical white fibrotic endometriosis lesion (double arrow) immediately over the left ureter and left ovarian fossa in a 16-year-old patient with stage II endometriosis

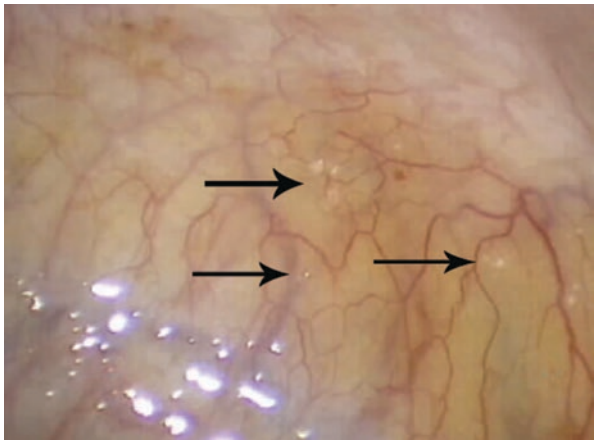

Fig. 3.4 Atypical clear endometriosis lesions studding the peritoneum of the posterior cul-de-sac. The clear, vesicular, superficial lesions (arrow) were found in an 18-year-old patient with stage I endometriosis who had a family history of the disease

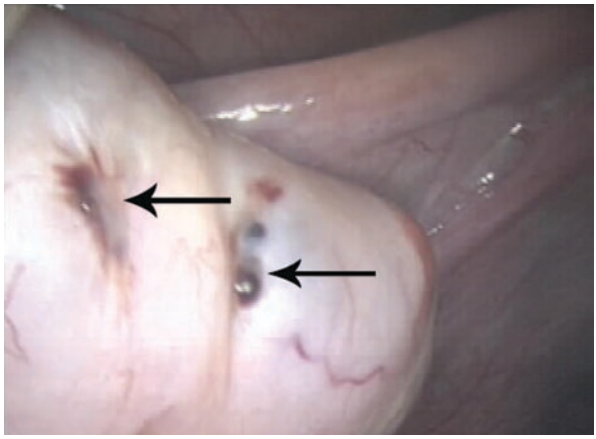

Fig. 3.5 Cortical endometriosis lesions (arrow) on the left ovary in a 15-year-old patient with stage III endometriosis

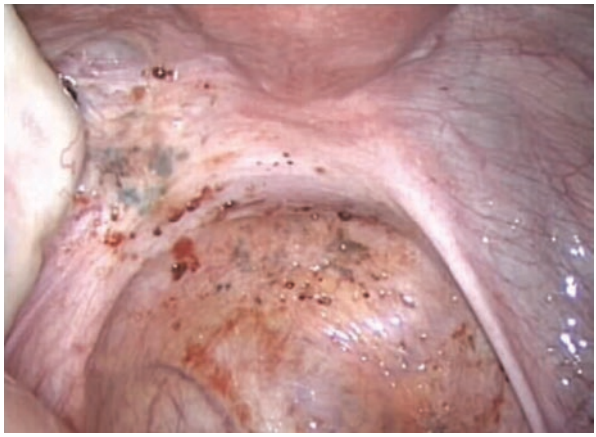

Fig. 3.6 Scattered variable-appearing endometriosis lesions with severe disease in the left pelvis. The endometriosis invaded the retroperitoneal fibroadipose tissue of the left posterior cul-de-sac and also involved the left paraureteral region. This extensive disease presentation was found in a 15-year-old patient with stage III endometriosis (the patient shown in Fig. 3.5)

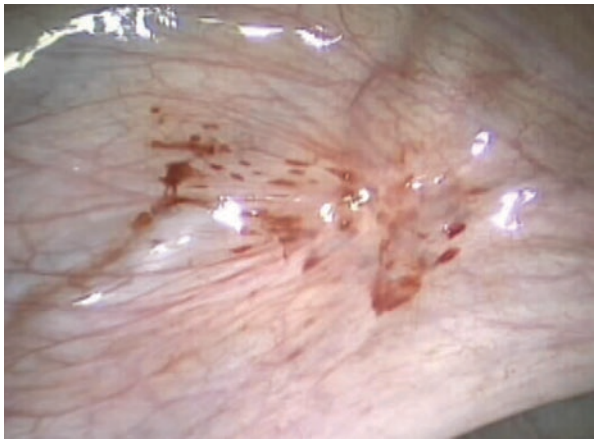

Fig. 3.7 Hemorrhagic red endometriosis lesions involving the left broad ligament and perivesicular peritoneum in a 20-year-old patient with stage II endometriosis

Table 3.4 Perioperative outcomes

Variable	*n* (%)
Endometriosis stage (*n* = 25)	
I	17 (68)
II	5 (20)
III	3 (12)
IV	0
Types of endometriosis lesions[a]	
Peritoneal defects	13 (68)
Atypical white/fibrotic	11 (44)
Atypical clear	6 (24)
Ovarian/cortical lesions	5 (20)
Hemosiderin/pigmented	5 (20)
Hemorrhagic	4 (16)
Miliary/nodular	3 (12)
Vesicular/endosalpingiosis	2 (8)

[a]Patients may have had more than 1

Table 3.5 Outcomes at 1 year

Outcome	*n* (%)
Postoperative medical treatment[a]	
COCs	16 (64)
Progestins	3 (12)
NSAIDs	8 (32)
None	3 (12)
Pain symptoms	
Successfully resolved pain	16 (64)
Improved pain	4 (16)
Continued pain	3 (12)
Recurrent pain	2 (8)
Length of follow up (months)[b]	20.0 (18.6); 0.5–58

[a]Patients may have had more than 1
[b]Data are presented as the mean (SD); range

Our study suggests that adolescents are overlooked because they may present with atypical symptoms of endometriosis. Vague abdominal symptoms, gastrointestinal distress, and genitourinary symptoms can confound the diagnosis of endometriosis, especially when the first healthcare provider the patient sees is not a gynecologist. In our cohort, the adolescents had an average 23-month delay in diagnosis from the onset of symptoms. Even after medical care was sought, almost a year was spent seeking appropriate diagnosis and treatment. Patients and their families appeared to self-advocate, with 44% of the referrals coming from the patients' mothers. This finding also highlights the potentially strong familial component of endometriosis, with 56% of patients reporting a positive family history in this patient sample [15].

Beyond missed school days and activities, adolescent females can be misdiagnosed with such conditions as PID and IBS, which can have adverse psychological impacts on them and may color their experiences with the healthcare system and how future healthcare providers view them. In our case series, the adolescents were evaluated on average by three physicians and referred to specialists such as psychiatrists and orthopedic surgeons before endometriosis was diagnosed. The delay in diagnosis decreased when the first physician who evaluated them was an obstetrician/gynecologist.

We advocate a see-and-treat approach for young women in whom medical therapy for dysmenorrhea has failed, because the prevalence of endometriosis is high in this population. Goals of surgical intervention are simultaneous diagnosis and conservative treatment to reduce the bulk of disease while decreasing pain and maintaining reproductive capacity. In our study, most of the adolescents had early-stage endometriosis, confined to the pelvis. This finding concurs with other studies that demonstrated that adolescent females have early-stage disease [3, 16, 17], that endometriosis may be a progressive disease, and that early diagnosis and ablation or removal of the affected tissue may decrease the long-term detrimental effects of the disease, including chronic pain and infertility [18, 19].

However, it should be noted that, in adolescent females, subtle atypical lesions such as those that are clear, white, or red are more common [4, 20, 21] and may be missed during laparoscopy if surgeons are looking for the powder-burn lesions that are commonly seen in adults. In fact, Vercellini et al. [4] visually diagnosed endometriosis in 40% of adolescent females with pelvic pain, but this percentage rose to 52% when atypical clear or red vesicular lesions were included. Familiarity with atypical lesions may help the physician to arrive at the correct diagnosis among adolescents. We have observed that adolescent females have clinical improvements in their endometriosis-associated pain symptoms, with good pain control at the 1-year follow-up after laparoscopic diagnosis and concurrent treatment with either resection or ablation and postoperative medical therapy. At 1 year, 80% of the patients in our study reported either resolved or improved pain after surgery. Although we do not have 5-year follow-up data, Tandoi et al. [22] reported a 56% recurrence rate at 5 years, and 34% of their adolescent cohort underwent a second laparoscopy to treat recurrent symptoms [22].

The strength of our study is the number of adolescent females from our tertiary referral center and the inclusion of data regarding referral and prior diagnoses and treatment. It examines possible etiologies for the delay in diagnoses and emphasizes the atypical symptoms and atypical endometriosis lesions found in adolescents. The primary weaknesses are the retrospective study design and lack of ability to control the data collection including standardized pre- and postoperative validated pain assessments. The population itself, consisting of primarily white females at a tertiary referral center, limits the generalizability of the study. Recall bias is another limitation to data collection regarding the patients' previous diagnoses, physicians, and prior treatments. Another weakness is the varied postoperative treatments. This variation prevents us from differentiating whether the surgery and/or postoperative treatment affected the patients' postoperative pain outcomes. In addition, the descriptive nature of the case series precludes the ability to draw significant conclusions about our findings.

Future work will focus on prospective studies examining the relationship of early diagnosis and treatment with pain and fertility outcomes. We also hope to examine the association between diagnosis at an early age and a familial form of endometriosis, since many in the study had a positive family history of endometriosis. Finally, we would like to conduct a prospective study to learn whether excision versus ablation is associated with better postoperative pain and fertility outcomes.

Conclusion

Adolescents with severe pelvic pain and no historic or radiographic evidence of pathology have a high rate of endometriosis. Thus, endometriosis should be strongly considered in adolescent females with pelvic pain refractory to medical management. Nevertheless, it must be emphasized that medical management is the first-line therapy and only after a sufficient trial of medical therapy should surgical

management with laparoscopic evaluation and treatment be pursued. The findings of this descriptive study suggest a potentially long and tortuous road to appropriate diagnosis and treatment. It also highlights the initial challenges that young females with endometriosis encounter. Therefore, timely referral to a gynecologist who is experienced with the laparoscopic diagnosis of endometriosis in adolescents and conservative treatment may significantly benefit their future quality of life.

Disclosures Dr. Nezhat is a medical advisor to Plasma Surgical, Roswell, GA, and a consultant to Karl Storz Endoscopy-America, Inc., El Segundo, CA, and is on the Scientific Advisory Board of SurgiQuest, Milford, CT.

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Part II
Endometriosis Definition

Chapter 4
Defining Endometriosis for Doctors and Patients

Sara Carvalho and António Manuel Setúbal

Introduction

The prevalence of endometriosis is considered to be more than 10% in women of reproductive age. Nevertheless, for adolescents, this prevalence is more precise. Studies report between 25 and 38 percent for adolescents with chronic pelvic pain [1, 2], 47 percent for those that undergo laparoscopy [3], and 50 to 70 percent [4–6] in cases where symptoms are not controlled with oral contraceptives and nonsteroidal anti-inflammatory drugs.

But why is the diagnosis so difficult to make? Why do doctors, even those that specialize in this condition, continue to "speak different languages" as regards the use of specific terminology? The impact of this terminological dispersion is real and can hamper the overall communication with patients. Therefore, it is important that experts "speak the same language." Doctors need time to talk to patients in order to explain what endometriosis is and tackle its complexity. However, they also need time to listen to them. As stated by Lone Hummelshoj (chief executive of WES, World Endometriosis Society), "(…) it is very important to have time to listen to the patients and to explain the illness well to them (…)."

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Since a detailed account on the early history of endometriosis is put forward by the Nezhat's in Chap. 2 [7], this chapter aims to provide some reflections and strategies for doctors, for patients, as well as for the adolescent patients' families, in order to promote clearer communication among the different stakeholders related to endometriosi. It is believed that communicating more effectively may help reach an early diagnosis and, perhaps, contribute to a more adequate management of this condition.

Finding the Right Way to Talk About Endometriosis: Making Every "Word" Count

Anna was 14. And with her first period, about 2 years ago, the nightmare had started: debilitating cramps, severe nausea, and her belly so swollen that she looked pregnant. She had actually fainted twice at school. "These teenage girls hardly eat anything these days," her History teacher had said. On "those" days, it seemed as if she had been hit by a truck or a train. She had tried to talk to her girlfriends about this, but it wasn't easy. You don't usually talk about your menstrual cycles with your friends, even among girls. That's just weird. Period. At home, things weren't much better. Whenever she told her mom that the pain was getting worse, that the hot water bottle solution was just not working anymore, and that this couldn't possibly be normal, she always heard the same response: "I went through the same thing, and so did your Aunt Lydia, your grandma...Sorry, sweetie, but this seems to run in the family. I'm sure you'll get better when you get pregnant. That's what happened to me." After a while, Anna eventually started thinking that this was, in fact, all in her head. Maybe she was exaggerating. Maybe this was normal after all.

But one day, she came across a leaflet that was just lying there on one of the tables at the high school cafeteria. Endometriosis. Endo…what? She started reading the headlines: severe pelvic pain, pain during sexual intercourse, nausea, pain while defecating…And then, in all caps: "MENSTRUAL PAIN IS NOT NORMAL!" Sweat started pouring down her forehead. She immediately knew it. She felt it. This was it. She wasn't crazy. She wasn't the only one.

After a quick Google search on her mobile phone, she started panicking. No cure? Infertility? Surgery? Then all these odd words: endometrioma, dysuria, laparoscopy, hysterectomy…. She felt overwhelmed. With insecurity, fear, anxiety, stress…Who could she talk to? There was a phone number on that leaflet, of some patient association that helped women with this disease, but she wasn't just going to call someone she didn't know, out of the blue. Who would take a 14-year-old seriously? She decided to take the leaflet home, and that evening, she told her mom about it. "Don't be so melodramatic, Anna," her mom had replied after reading the brochure. "I know you have painful periods sometimes. Believe me, I've been through the same thing, but surgery? Infertility? Come on, I've had you and your sister! How could that have been possible if I had that endo…something? But if it

makes you feel better, we're visiting Dr. Jones the day after tomorrow. He's been our GP ever since you girls were born. He knows you better than any other doctor."

"There's nothing wrong with you, Anna," Dr. Jones had stated in a somewhat soothing voice. "But I read about this disease called endometriosis, and I think that's what I have! Look at my belly! Look how swollen it is! I'm only able to be here because I took painkillers! You can't possibly tell me this is normal!" A feeling of helplessness started creeping in, and Anna couldn't help but cry. "Come on, Anna, be reasonable. Dr. Jones is trying to help you…us. He's the doctor, not you. You know you can't believe everything you read online. I'm sorry, Dr. Jones. You know how moody teenage girls can be."

On the way home from the doctor, Anna never said a word. She felt lost, betrayed. Her mom had been through the same thing, apparently. Why couldn't she stand up for her own daughter? Anna's mind was made up. She wondered where she had placed that leaflet, but she would search online for information on that patient association. She would call them. They would listen, right?

Later that night, Anna woke up in so much pain she thought she was going to die. Screaming in agony, she went to the local hospital where she heard that some cyst had burst, and she had to undergo an emergency laparotomy. A few days later, when she came home, she learned from her mom that her left ovary was gone. "You were right. Apparently, it was that endometriosis thing. But the doctors said you'll still be able to have children. And they confirmed that in many cases, pregnancy can cure the disease."

The story of this fictional character is, regrettably, very much true for many adolescents worldwide. Despite its considerable prevalence and significant economic and social impact [8, 9], endometriosis is still relatively unknown, even among healthcare professionals, and somewhat underrepresented in the media. Therefore, one of the main challenges for those who are involved in raising awareness about this condition and/or managing it, both from a medical and surgical perspective, is how to effectively disseminate the knowledge that currently exists among the several stakeholders: healthcare providers in various specialties, but also – and mainly – patients, their families, other caregivers, as well as society in general.

This challenge becomes even more demanding at a time when technological innovation has dramatically shaped where, when, and how we have access to information. In the healthcare setting, it is difficult to compete against Dr. Google, ever more ubiquitous and omniscient, and to separate the wheat from the chaff as far as what sources can be classified as trustworthy. On the other hand, patients are more and more willing to take the driver's seat and play an active role in all matters related to their health. In fact, health literacy, defined as "the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information and services to make appropriate health decisions,"[1] has been one of the key drivers of twenty-first-century healthcare. Nowadays, it is common

[1] https://www.cdc.gov/healthliteracy/learn/index.html

to have patients themselves collect and, in some cases, share their health data with healthcare providers, which, very often, helps to further develop the research being conducted on a number of medical conditions. Yet the more involved patients become in managing their own health, the more they demand to know and own as regards their personal data, which poses a number of questions and dilemmas to the healthcare sector.

This is no different for the several actors involved in and related, one way or another, to endometriosis. As in most cases, communication is key. Even though we human beings usually change the way we interact with one another depending on socioeconomic, linguistic, educational, professional, or even age-related factors, there must be some common ground on *what* is being discussed so that effective communication can take place. Given the enormous complexity that characterizes endometriosis, it is not always easy to find the right "words" to talk about it and to adapt that content to different types of target audiences while maintaining linguistic and conceptual accuracy. And this rationale applies both to *healthcare professionals and to the way they communicate with each other*, as well as to the interaction between *these professionals and the patients*. However, in order to come full circle in spreading the word and increasing health literacy on endometriosis, it is also essential to address *patient to professional* and *patient to patient communication*, especially via the mediation of patient associations and organizations. The sections that follow will focus on these three levels of interaction.

The Professional-Professional Communication: The Importance of "Speaking the Same Language"

Similar to how the role of operative video laparoscopy was continually redefined during the 1980s and 1990s due to its rapid progress and adoption for complicated cases – removal of large uteri, severe adhesions, endometriosis, cancer, pregnancy, etc. – [10], endometriosis is frequently regarded as an enigmatic disease, even among the medical community. As regards its pathogenesis, several theories to what might cause this condition have been put forward [11, 12], yet none has been fully accepted, largely because the knowledge about the disease has been changing and evolving very rapidly. Moreover, the various signs and symptoms are often mistakenly associated with other conditions, such as irritable bowel syndrome or interstitial cystitis. In addition, there is currently no standardized classification of the disease that can accurately reflect its complex nature [13]. Moreover, endometriosis is still poorly represented in many medical curricula all around the world. As a result, it is not surprising that a lot of physicians, including gynecologists, are still rather unfamiliar with this medical condition. The situation is particularly sensitive in the primary care setting since general practitioners (GP) are usually the first line of response, especially in the case of adolescents. Nezhat et al. [14] found patients (n = 25) with a mean age of 17.2 had experienced symptoms for an average of

22.8 months and seen a median number of three physicians before receiving an accurate diagnosis.

On the other hand, a multifaceted disease requires a multifaceted team of healthcare professionals, which implies that not only gynecologists but also urologists, gastroenterologists, medical imaging experts, physical therapists, psychologists, and other experts are involved in the process. Given the diversity of academic and training backgrounds, as well as the different levels of expertise, ensuring that all these healthcare professionals can communicate in a clear and consistent way is critical. Since inconsistencies and ambiguity are an inherent part of natural language, one way to address some of these communication challenges is to stabilize the terminology of the subject field, i.e., knowing which term(s) can – as unambiguously as possible – designate the concepts A, B, or C [15]. This will undoubtedly bring added value to the area in question by contributing to a more effective representation, organization, and sharing of the core specialized knowledge about endometriosis [16].

One of the areas where this streamlined specialized communication can have the most profound impact is the disease diagnostic (where the delay is currently of 6.7 years on average [17]). And in this respect, specialized training plays a fundamental role, especially in the primary care setting, one of the main targets of such training actions. With the latest technological advances in surgical video, for instance, the development of tailored multimodal materials, featuring text-based content, but also image and video (mostly intraoperative) footage, can provide a more comprehensive view of the disease to those professionals that may deal with endometriosis at an early stage. More recent initiatives, such as the widespread use of Electronic Health Records (EHR) across different medical providers, across different institutions, and even across different countries [18], rely on an effective professional to professional communication as well. All in all, expert agreement on a solid terminological foundation in this subject field should not be underestimated. It is crucial that the various professionals that deal with endometriosis are able to "speak the same language."

The Professional-Patient/Patient-Professional Communication: The Importance of "Speaking the Right Language"

Perhaps the biggest challenge when it comes to communication in the healthcare setting lies in the interaction(s) between healthcare professionals and patients, especially those that occur face to face, as is the case of medical appointments. It is, indeed, a rather complex social interaction as it involves a set of variables.

The medical professional, for one, has the knowledge and different levels of expertise – concerning, in this case, endometriosis – that he/she wishes to transmit to the patient. However, these professionals can be so caught up in the medical

jargon that characterizes their everyday activities that it is not always easy for them to find the balance between technical and plain language. On the one hand, they must be able to explain the disease, its signs and symptoms, necessary exams, procedures, as well as medication in a way that most patients can understand. On the other hand, it is also advisable that they introduce more specific terminology to the patients so that they can start entering the enigmatic realm of endometriosis and finding more accurate information about this complex disease. Additionally, there are generally time constraints, so whatever information needs to be exchanged, this must be done in a limited amount of time.

As for the patient, the situation is also not exempt from complexities. No patient is the same: people differ in age, nationality, socioeconomic status, medical history, qualifications, beliefs, cultural behavior, just to name a few factors. When faced with a diagnosis of endometriosis and after the initial shock, a lot of questions will surely emerge in the patients' heads, but their reaction and subsequent interaction with their doctor can vary greatly. Some patients may tentatively try to interact with their physician, while others may not even do that at all, due either to the fear of asking a "stupid" or "basic" question or to the ingrained belief that doctors know best. Some may think that asking a question might be perceived by the doctor as questioning his/her competence. Some may have actually heard that from another doctor in the past and may come to the realization that as patients differ, so do healthcare professionals. Others may arrive at the medical appointment armed with questions and with several hours of prior research. From those, some may have the necessary skills to navigate the flood of online information, both from accurate and inaccurate sources, others perhaps not so much. Some endometriosis patients may also have high-level qualifications (master's degrees or PhDs), a few even a healthcare-related background. All of this poses additional challenges to the professionals, especially in this new era of patient-centered healthcare [19].

The situation is even more complex for adolescents. They are the ones with the disease, but depending on the country and culture, their legal status and freedom as to what decisions they may or may not make over their own body can be extremely limited (or even nonexistent). Some adolescents may also have to struggle with the lack of support, both at home and at school. Others may be able to count on a relative to be there for them, but that person may not have the necessary health literacy skills to actually be able to make the important decisions in an informed manner.

In such an intricate framework, it is crucial that healthcare professionals can "speak the *right* language" when communicating directly with the patients and their families, trying to find a balance that is not always easy to achieve. However, the opposite also applies: patients should also work on improving the quality of that communication, namely, by participating actively and constructively in their own healthcare process. Finding that balance is critical. Informed consent forms are good examples of how such a balance could be and needs to be reached, for the sake of fostering health literacy. These forms usually contain a high percentage of technical language. While it is understandable that that happens, it is more difficult to accept that such a document may not also comprise a plain language summary or, at

least, an explanation/a paraphrase of the main technical terms. Given that patients (or a next of kin, as is often the case with adolescents) have to sign an informed consent before any major exam or procedure, it is their right to know exactly what is being described in that form.

Overall, professionals as well as patients want the same as regards endometriosis: to fight the disease, to improve the quality of life of the affected women/girls, and to raise awareness. But the reality in what concerns access to information has changed dramatically, so expectations, roles, and behaviors have to adjust accordingly. Endometriosis patients will search for online information regardless of what their doctors tell them. So healthcare professionals should use that to their advantage by recommending reliable sources and informing patients about national or local support organizations. That way, medical appointments can become more productive and enriching. And this is also another step from both parties toward finding the "*right* language."

The Patient-Patient Communication: The Importance of "Speaking 'My' Language"

Given that patient empowerment is becoming more and more widespread, as referred to earlier, it is no wonder that the number of endometriosis support groups and patient associations has experienced substantial growth in recent years. According to the well-known platform endometriosis.org,[2] there are at least 50 official endometriosis associations around the world. The number of informal patient support groups is more difficult to determine, but a quick search on Facebook for "endometriosis support" (in English) in January 2019 resulted in approximately 120 pages and 100 groups in total, some of the latter containing more than 10,000 members each. The Worldwide Endometriosis March (EndoMarch),[3] one of the most successful and impactful events worldwide, is currently being organized in more than 50 countries, mainly by patient associations. EndoMarch was founded to empower women to take their healthcare into their own hands, to raise awareness of endometriosis, and to promote research and treatment of endometriosis.

This vibrant and engaged community constitutes an essential partner in the global fight against endometriosis, especially because these associations and groups are able to speak *the patients' language*. They actually know what the patients are going through, and they know their fears and doubts. They help the patients feel that they belong sometimes at a stage of their personal journey where many women/girls are not taken seriously, not even by their own families. Through their daily work with all kinds of patients, as well as with families and other caregivers, these

[2] http://endometriosis.org/support/support-groups/

[3] This initiative was founded in 2013 by Drs. Camran, Farr, Ceana, and Azadeh Nezhat to "empower, educate and effect change." Cf. https://www.endomarchnews.org/

associations are able to get a comprehensive glimpse of local and national needs that very few of the remaining stakeholders have.

This extensive field of knowledge can provide extremely valuable input to the creation of endometriosis resources targeted not only at patients but also – and most importantly – at other groups, namely, primary care institutions and schools. As regards specifically adolescent endometriosis, one must bear in mind that there are at least four potential – and very different – target groups, each with its own profile: the adolescents themselves, their families, teachers, and, in cases where this exists, school nurses/medical staff. In this case, and for dissemination purposes, one size clearly does not fit all: it's crucial that the awareness initiatives and materials can be customized as far as content, level of (in)formality, or even medium are concerned, all while maintaining their scientific accuracy and remaining appealing to each one of those groups. In multilingual contexts, which is the case in more and more countries, the choice of the language(s) is also key. All of this implies a close collaboration between patient associations and endometriosis experts in order to guarantee that scientific and linguistic consistency. Fortunately, this collaboration is already quite visible all around the world, but as long as there are endometriosis patients waiting for their due diagnosis, the work cannot stop.

In this quest for raising endometriosis awareness, MulherEndo, the Portuguese Association for Women with Endometriosis,[4] founded in December 2013, has recently decided to take things one step further: within the scope of a project supported by national funding,[5] a group of patients is currently attending online certified training focused solely on endometriosis and delivered by some of the top experts on this field at a national level. The ultimate goal is to further empower those patients and prepare them to give informative lectures in schools or primary care institutions, as well as to create more comprehensive supporting materials.

While there is no specific target on health literacy within the Sustainable Development Goals (SDGs) published by the United Nations, efforts to raise health literacy, especially among patients, their families, and their supporting communities, will be crucial for the full realization of the 2030 Agenda for Sustainable Development.[6] As a result of MulherEndo's experience in organizing lectures, as well as Q&A sessions at schools, adolescents and their families have been identified as two priority target groups. It is expected that this tailored approach can help bridge the gap in what concerns the diagnostic delay described earlier and, in addition, empower adolescents who struggle with the disease, eventually contributing to

[4] http://mulherendo.pt/

[5] POISE-03-4639-FSE-000084 (http://poise.portugal2020.pt/)

[6] https://sustainabledevelopment.un.org/

more active and vocal patient advocates in the near future, advocates that can speak the patients' voice.

Conclusion

This chapter aimed to reflect on the idea that while one should devote all efforts to trying to learn more about such a complex disease as endometriosis, it is also crucial to dedicate some time to *what* we *say* about the disease, *to whom*, and *how*. On the one hand, it is essential that more and more healthcare professionals at various levels – from primary care settings to expert centers – learn and talk about this disease so that they can "speak the *same* language" and, therefore, collect, organize, and exchange patient information in a more efficient and reliable way. But communication between these professionals and patients (and vice versa), as well as communication within patient communities, is also critical. Speaking the "right language" by being able to effectively integrate technical and plain language reaches people's eyes and ears. But speaking the "patients' language" in a way that is personal – not melodramatic – and still accurate reaches people's hearts.

Together with healthcare providers, patients and patient communities can – and are eager to – help spread the word and increase health literacy on endometriosis. It is therefore essential that the various experts and patient associations work collaboratively on the right tools and resources as the clock is indeed ticking for all the women/girls waiting for their endometriosis diagnosis. It is important to make each second count and leave no one behind.

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Part III
Etiology of Endometriosis

Chapter 5
Molecular Mechanisms Underlying Adolescent Endometriosis and Advancements in Medical Management

Saifuddin T. Mama

Introduction

As discussed in Chap. 2, reports of symptoms today associated with endometriosis have been documented since ancient Egypt (1855 BC) and have long been inaccurately named or attributed to strangulation or suffocation of the womb, supernatural forces, hysteria, and more recently irritable bowel disease (IBD) [53]. Today, we know endometriosis is an estrogen-dependent inflammatory disease. Hormonally responsive endometrial tissue is located outside the uterus in the pelvic and abdominal cavity. Initially, it is a disorder with ectopic cells measuring <1 mm^3; eventually, there is progression toward a disease state with these cells surviving and adhering to intact mesothelium. These then proliferate and invade along with accompanying neovascularization [1, 2]. There is altered cell signaling, the development of proinflammatory pathways, impaired cell immunity, and impairment of natural clearance by the immune system leading to proliferation and invasion of ectopic endometrial tissue. It is a progressive, chronic disease with wide symptomatology and no cure and requires long-term medical and surgical management as well as ongoing psychosocial support [24]. It results in severe and chronic morbidity. The long-term sequela of inflammation, scarring, and adhesions is expressed as cyclic and acyclic pelvic pain that invades all aspects of the patient's life, with dysmenorrhea, dyspareunia, tenesmus, dyschezia, pelvic and abdominal bloating, and accompanying nausea and vomiting all of which severely limits normal activity with resulting absences from school and work. In adolescent females, the delay in diagnosis ranges from 2 to 12 years averaging 7 years, and it is commonly reported that

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the symptoms are trivialized, normalized, or dismissed by society and health-care providers [3, 4, 54]. Nezhat et al. found patients (n = 25) with a mean age of 17.2 had experienced symptoms for an average of 22.8 months and seen a median number of three physicians before receiving an accurate diagnosis [54]. The level of awareness of endometriosis symptoms is low in adolescents. The disease has been noted in premenarchal girls, and blind biopsies of normal peritoneum have been positive for the disease [5, 6]. In teenagers undergoing laparoscopy, a 47% incidence has been reported [48]. The prevalence rate in adolescents with chronic pelvic pain is 25–29% [4, 7], and in patients undergoing laparoscopy for pain refractory to medical treatment, the prevalence is 33–75% [4, 7–9]. It is the single leading cause of morbidity in premenopausal women [13]. In adolescence, lower stages of endometriosis have been reported to be less responsive to surgery, with a significant recurrence of pelvic pain [49] and a repeat surgery rate between 22% and 34% [50, 51].

Cyclical pain progresses to acyclical pain, eventually presenting throughout the month with endometriotic lesions promoting nerve proliferation, hyperinnervation, and neural remodeling with increased stimulation of mechanoreceptors innervated by unmyelinated C afferent and myelinated Aδ fibers [17, 35]. Patients without endometriosis have very small numbers of C nerve fibers. Peritoneal adhesions, often seen in patients with endometriosis, have been shown to be innervated and contain sensory nerve fibers [46]. Depth of lesion is associated with increased level of pain, but there is no relationship between the extent or location of disease and severity of pain [4]. Lesions seen in the peritoneum in endometriosis are white, yellow-brown, red, red-pink, clear, black, and blue-black lesions. Red lesions are usually highly vascularized active lesions representing early disease; white lesions are opacified, devascularized with old collagen representing quiescent disease; and yellow-brown lesions represent latent endometriosis with inflammation and fibrosis. The final stages of the embedded endometrial implant provoking a fibromuscular reaction with scarring are black and blue-black lesions, implants with intraluminal blood, breakdown products of blood, and elements derived from cell damage.

Inflammatory bowel disease, rheumatoid arthritis, asthma [18], migraines [19], psoriasis [20], and thyroid disorders have been associated with endometriosis [55–58]. The intriguing possibility of neonatal uterine bleeding seeding progenitor cells into the pelvic cavity activated at adrenarche has been proposed [10]. Primitive endometrium has been found outside the uterine cavity in a postmortem study of fetuses [11, 28]. There are no diagnostic markers that are appropriately specific and sensitive for use in endometriosis diagnosis.

Genetics and Epigenetics

Endometriosis appears to be a polygenic and multifactorial disease. The prevalence of endometriosis in relatives of patients with the disease is higher than the normal population with the risk increasing 7- to 10-fold. Studies with twins also suggest a

genetic component associated with the disease [31, 32]. Some studies suggest a linkage to chromosomes 7 and 10.

Epigenetics in endometriosis involving phenotypic changes with stable gene expression is an area of intense investigation, and there is mounting evidence of its role in pathogenesis of endometriosis. Regulation of genes via remodeling of chromatin with modification of histone proteins via DNA methylation and covalent histone modification, respectively, acting in concert dynamically controls chromatin structure and gene expression. DNMT variation in gene expression plays a part in endometriotic cell-specific DNA methylation patterns; all three genes (DNMT1, DNMT3A, DNMT3B) coding for DNA methyltransferases involving genomic DNA methylation are overexpressed in endometriosis [33].

HOXA genes, as regulators providing body segment identity in embryonic morphogenesis, are expressed differently in the upper vagina (HOXA-13) as compared with HOXA-10 in the uterus or HOXA-11 in the lower uterine segment and cervix [41]. The HOXA10 promoter in the endometrium of women with endometriosis is hypermethylated compared to women without endometriosis; this reduction in gene expression may be responsible for reduced fertility in women with endometriosis. It is normally dramatically increased in mid secretory phase of the menstrual cycle. HOXA-11 expression is also reduced in patients with endometriosis.

MicroRNAs are nucleotide noncoding RNA sequences that bind specifically to target mRNAs repressing their translation into proteins. Regulation by microRNAs has been reported at the posttranscriptional level [38]. Multiple studies have identified microRNAs as aberrantly expressed in endometriotic lesions [38, 39] with several unique microRNAs present in endometriotic epithelial cells which are not found in the surrounding healthy tissue [12]. As outlined below, TGF-β1, COX2, VEGF, aromatase, and estrogen are modulated by microRNA activity. Endometriosis-associated microRNAs that affect mediators of cell proliferation are expressed (either over- or underexpression) opposite to the differential expression in cancer [44]. Messenger RNA microarray studies in endometriosis patients show an upregulation of tumor suppressor genes and downregulation of mRNAs associated with cell cycle progression [45]. Further, microRNAs in the future may represent possible diagnostic markers for endometriosis. These studies above provide a compelling argument for epigenetics playing a role in endometriosis.

Etiology

Various theories for histiogenesis include metastasis theory with retrograde menstruation, hematogenous spread, lymphatic dissemination, and iatrogenic dissemination. Ectopic endometrial tissue is seen in dependent parts of the body, mainly the pelvis, implanting and eliciting a chronic sterile inflammatory response with loss of self-tolerance and eventual remodeling of the mesothelium [1, 2, 12].

There is common embryonic tissue for ovarian germinal, mullerian, and peritoneal mesothelium. This has led to the coelomic metaplasia theory, the underlying

concept being germinal epithelium of the ovary and serosa of the peritoneum are transformed by metaplasia into endometrium, but there is less evidence for this process of dedifferentiation of mesothelium. This is not seen more frequently in men which would be the case if peritoneal cells undergo metaplastic transformation, the frequency does not increase with advancing age, endometrial implants are not uniformly distributed in pelvic peritoneum, and there are not an equal amount of implants in abdominal peritoneum. Endometriosis seen in adolescents before or just after menarche suggests that embryonic mullerian tissue may play a part via aberrant differentiation or migration [27]. The ovaries are involved in roughly half of all women diagnosed with endometriosis with unique development of endometriomas and requires a classification system of its own. Nezhat et al. observed in a series of 187 women, superficial ovarian endometriosis acts similarly to endometriosis of extra-ovarian sites. Large endometriomas, however, can develop as a result of secondary involvement of functional ovarian cysts via the endometriotic process [59]. One theory for endometrioma formation is inversion and progressive invagination of the ovarian cortex; alternatively, metaplasia of the coelomic epithelium of the ovary has been suggested. Similarly, the induction theory of late growth of persistent embryonic rests also has less evidence [2]. It assumes embryonic rests persisting into adulthood along the sites of the migration pathway of the embryonic mullerian system. Deep endometriotic nodules, particularly in the rectovaginal septum being retroperitoneal, may represent a distinct entity from peritoneal endometriosis lesions. It has been suggested in genome-wide association studies that early versus advanced stage disease represents different entities [4].

There appears to be either constitutive or acquired molecular alteration of ectopic endometrium combined with deficient or altered immunity [13]. The normal ability of the immune system in blocking the development of endometriosis is diminished. This allows proliferation of ectopic endometrial tissue with possible clonogenic activity [12]. The endometrium has been shown to have a rare population of cells with stem cell characteristics with clonogenic activity. These endometrial-like mesenchymal stem cells (eMSCs) show an increased clonogenicity in the proliferative stage for stromal cells and in the secretory stage for epithelial cells [37]. It is possible that misplaced eMSCs in retrograde menses may play a role in establishing early endometriotic lesions. Separate from eMSCs, endometrial regenerative cells (ERCs) that resemble eMSCs have been isolated; these express matrix metalloproteases (MMPs) specifically MMP-3 and MMP-10, the angiogenic factor Ang-2, and cytokines.

The overall ability of ectopic endometrial tissue to survive, proliferate, invade, and induce angiogenesis is the sequence seen in disease progression. Pathologic findings in patients with endometriosis visible on laparoscopy range widely, including the classic endometrial glands and stroma, fibroconnective tissue, chronic inflammation, reactive mesothelial cells, hemosiderin deposition, endosalpingiosis, and adhesions. The natural progression of the disease leads to fibrosis with the chronically inflamed peritoneum undergoing changes in architecture.

Cellular and Molecular Mechanisms

Reflux Retrograde Menstruation

Described by Sampson [29], it assumes that retrograde menstruation occurs with viable ectopic endometrial tissue regurgitated through the fallopian tubes. In the perimenstrual period, on laparoscopy, the majority of patients had blood seen in the posterior cul-de-sac [12]. Since peritoneal fluid in the abdomen flows in a counterclockwise manner, more endometriotic lesions have been seen on the right versus the left side of the diaphragm corresponding to the barrier formed by the falciform ligament [30]. Dispersal of cells via lymphatics may be the origin of distant lesions in the thorax or other extraabdominal sites.

Ectopic Endometrial Cell Adhesion, Attachment, and Invasion of Mesothelial Lining with Degradation of Extracellular Matrix (ECM)

There is a permissive peritoneal environment. Peritoneal fluid from women with known endometriosis has been shown to enhance ectopic endometrial cell proliferation [36]. The attachment of ectopic endometrial cells to intact mesothelium occurs within 1 hour, and transmesothelial invasion occurs within 24 hours. This suggests that intact mesothelium is not a defense barrier for adhesion of ectopic endometrial tissue [1]. Some endometrial epithelial and stromal cells have mesenchymal stem cell-like differentiation potential [12]. Endometriosis progression itself is associated with an epithelial-to-mesenchymal transition, the mesothelial lining undergoing morphological alteration [2, 15]. There are a large number of cell adhesion molecules (CAM) expressed by ectopic endometrial cells. These include integrins being transmembrane glycoproteins acting as anchors for the cells to the extracellular matrix-mediating cell matrix adhesion and are involved in direct invasion of cells into the mesothelial lining. Their expression is highly variable. Integrin β3 is always absent in the endometrium of women with endometriosis. Cadherins as calcium-dependent transmembrane glycoproteins mediate cell-to-cell interactions, and the endometrial cell epithelial-cadherin system is deregulated in patients with endometriosis. E-cadherin has been shown to be downregulated and essentially absent in ectopic endometrial cells due to hypermethylation and inactivation, and since it functions as an intercellular adhesion and metastasis suppressor protein, its deregulation is likely associated with invasiveness of endometriotic cells [34]. E-cadherin protein is present in the glandular cells of eutopic endometrium. Cadherins are controlled by cytokines including epithelial growth factor (EGF) and hepatocyte growth factor (HGF). Activation of these growth factor receptors promotes transition from the epithelial to mesenchymal cell transition. Laminin binding proteins also modulate cell-to-cell attachment [2].

The ECM which acts as a scaffold for proliferating glandular and stromal cells is composed of collagens, proteoglycans, and glycoproteins including fibronectin and laminin. The ECM undergoes breakdown and remodeling mediated by MMPs. MMP-2 is increased which degrades type 4 collagen. MMP-9 is also increased and is involved in vascular growth. MMPs are induced by inflammatory cytokines, growth factors, and hormones including interleukin-1 (IL-1), IL-6, tumor necrosis factor α (TNFα), EGF, platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). PDGF promotes cell proliferation by autocrine interactions. Transforming growth factor-beta1 (TGF-β1) regulates cell proliferation, differentiation, and angiogenesis and affects the immune response. It regulates vascular endothelial growth factor (VEGF). It is expressed in endometriotic lesions and, via VEGF, plays a role in endometriosis formation [13]. TGF-β1 acts as a mediator of progesterone suppression of MMPs and enhances expression of tissue inhibitor of metalloproteinases (TIMPs). It is critical in tissue remodeling. Patient with endometriosis have higher levels of TGF-β1 in the peritoneal fluid. TGF-β1 bioavailability and signaling are modified by microRNAs miR-200b, miR200c, miR-141, and miR-21 [2]. Another family of proteases, the plasminogen/plasmin activation system is also involved in ECM breakdown. Plasminogen has been detected in high concentrations in ectopic versus eutopic endometrium.

Recent reports of ectopic endometrial cells releasing extracellular vesicles containing portions of membrane suggest another means for cell-to-cell communication with one study showing that endometriotic stromal cell-derived exosomes exerted angiogenic effects [40]. Local modulation of signaling pathways of cells and tissue by extracellular vesicles may contribute to adherence, invasion, proliferation, evasion of the immune system, and eventual progression into a persistent endometriotic lesion.

Proliferation of Tissue with Pro-inflammatory Pathways, Resistance to Apoptosis, and Neovascularization

For endometriosis progression with growth of ectopic tissue, multiple pro-inflammatory pathways play a part. Elevated levels are seen in estradiol, aromatase, cyclooxygenase (COX)-2, TNFα, prostaglandin E2 (PGE2), growth factors, cytokines, and angiogenic factors [15].

Growth factor TNFα produced by activated macrophages circulating in the peritoneal fluid increases proliferation of ectopic endometrial cells. TNFα enhances both fibroblast proliferation and collagen synthesis favoring adhesion formation and angiogenesis by generating further cascades of inflammatory cytokines [12]. TNFα significantly increases IL-6 in endometriotic stromal cells. Via nuclear factor κβ (NFκβ), TNFα upregulates COX2, and it has been shown to increase prostaglandin production.

MicroRNAs miR-19a and miR-16 are downregulated in endometriosis. Since COX2 translation is suppressed by these microRNAs, their reduced expression enhances COX2 production, thereby enhancing prostaglandin production and activation of the amplification cycle of elevated aromatase and COX2, in turn leading to enhanced estrogen levels.

Cytokines are synthesized by peritoneal macrophages, lymphocytes, ectopic endometrial implants, and peritoneal mesothelial cells. Their aberrant expression favors implantation, angiogenesis, and adhesion formation. IL1β is elevated in peritoneal fluid and is secreted by activated macrophages. This induces COX2 via activation of NFκβ which leads to prostaglandin PGE2 increase in turn activating aromatase, overall leading to inflammation. IL1β also mediates VEGF expression as well as T-lymphocyte activation and B-lymphocyte proliferation. Another two cytokines that are increased are IL-1α and IL-2 in endometriotic lesions and peritoneal fluid in turn modulating IL-6 secreted by macrophages. IL-6 regulates cell growth and angiogenesis. IL-6 alters fibronectin which favors attachment of ectopic cells and elevates levels of VEGF, macrophage-derived growth factor (MDGF), and monocyte chemotactic protein (MCP-1), the last three enhancing proliferation of fibroblasts and endometrial cells [13]. Fibroblasts secrete MCP-1 depending on the level of PDGF stimulation. High levels of MCP-1 stimulate macrophages secreting cytokines and growth factors and directly stimulates proliferation. MCP-1 has been found to be elevated in patients with endometriosis. IL-2 also promotes angiogenesis by inducing VEGF. Elevated IL-8, a potent cytokine derived from peritoneal macrophages and endometriotic cells, stimulates neoangiogenesis and vascularization and assists in endometrial cell adhesion. IL-15 from endometrial stromal cells stimulates growth and invasion and suppresses natural killer (NK) cells [13]. IL-15 produced by endometrial cells directly stimulates their growth and invasion and suppresses the activity of NK cells, allowing escape from immune surveillance. The chemokine Regulated Upon Activation Normal T-Cell Expressed and Secreted (RANTES) is a chemoattractant for cells mediating inflammatory cell chemotaxis with macrophage recruitment in large numbers leading to elevated IL1β along with recruiting phagocytic and chemotactic leukocytes, and there is increased production of RANTES by ectopic endometrial cells [13].

Activation of cytokine signaling in endometriosis tissue induces nuclear receptor activation supporting ectopic lesion growth. Dysregulation of nuclear receptors with altered levels and functioning in turn affecting modulation is associated with progression of endometriosis. A series of endometriosis-specific nuclear receptors have been identified. DNA methylation patterns in gene promoter regions in ectopic endometrial tissue differ from normal endometrium [15]. DNA cytosine-5-methyltransferase (DNMT) variation in gene expression plays a part in endometriotic cell-specific DNA methylation patterns. DNMT 2 levels are downregulated in endometriotic tissue, while DNMT1, DNMT3A, and DNMT3B are upregulated [33]. Steroidogenic factor (SF-1) which functions as a transcriptional factor in activation of multiple steroidogenic genes for estrogen biosynthesis is elevated in

ectopic endometrium with DNA hypermethylation of the SF gene in eutopic endometrial cells and hypomethylation in ectopic endometrial cells. The dysregulation of SF-1 gene expression is implicated in estrogen-dependent endometriosis progression [15].

Alterations in the progesterone receptor signaling pathways is associated with endometriosis disease progression. Posttranslational modification such as phosphorylation and acetylation of the progesterone receptor allows for dynamic responses to changes in hormonal, growth factor, cytokine, and environmental stressors. It also interacts with chromatin in an epigenetic fashion [2]. Clinically, progestins alone induce decidualization (differentiation of endometrial stromal cells) with subsequent atrophy; however, 9% of patients will be nonresponsive [14]. This known progesterone resistance may be due to loss of PR-B expression in endometriotic cells. This process of downregulation in endometriotic tissue may be due to hypermethylation of the PR promoter region leading to repression of transcription. Hypermethylation of the progesterone receptor (PR)-B is seen in ectopic endometrial cells with concomitant decreased expression. Conversely, it has been reported that in samples of the inner linings of ovarian endometriomas, expression of PR-B is elevated.

Endometriosis is a known estrogen-dependent disorder progressing to disease. There is altered expression of estrogen and progestin receptors in ectopic endometriotic tissue [14]. Endometriotic tissue has high concentrations of estradiol-17β and elevated aromatase. Macrophages particularly express aromatase. Aromatase is hypomethylated in ectopic endometrium but not in normal endometrium. Patients with endometriosis have aberrantly high aromatase expression [43]. Estrogen acts via ERα and ERβ receptors, members of the nuclear receptor superfamily. The ERα is required for both normal endometrial growth as well as growth of ectopic lesions. ERα knockout animals with surgically induced endometriosis develop fewer lesions versus wild type. Lowered ERα levels have been noted in endometriotic tissue with progesterone resistance. In that setting, ERβ is increased. The expression of ERα likely varies depending on the site of endometriosis. ERβ is markedly highly expressed in endometriotic tissue versus normal endometrium [15, 16]. Of the isoforms, ER β1 is elevated. Hypomethylation of the ERβ gene promoter increases ERβ gene expression in endometriotic tissues compared with the normal endometrium. ERβ binds to the promoter region of the ERα, suppressing ERα expression in endometriotic cells. ERα deficiency in endometriotic cells may be responsible for the failure of estrogen to induce progesterone receptor gene expression. Increased ER sensitivity with a shift and increase in the ERβ/ERα ratio shifts E2 stimulation to E2 inhibition of progesterone receptor expression enhancing progesterone resistance [14, 15]. There is an altered response to progesterone. Additionally, VEGF is upregulated by the increased estradiol. Estrogen activity is highly regulated by microRNAs as is aromatase.

There is resistance to induction by progesterone of the enzyme 17β-hydroxysteroid dehydrogenase type-2 [42]. The activity of 17β-hydroxysteroid dehydrogenase-2 is reduced, diminishing the ability to protect tissue from high levels of biologically active estradiol (E2) [14, 16]. This in turn increases fibroblast production along with

increased expression of bFGF by endometrial cells. Elevated estrogen stimulates COX2 which in turn stimulates PGE2 which in turn is an important stimulator of aromatase activity in endometriosis. There is further conversion from androgens to estrogens by aromatase as another positive feedback loop cycle combining with the reduced 17β-hydroxysteroid dehydrogenase type-2 expression to further increase estrogen synthesis.

Prostaglandin concentrations are increased in the peritoneal fluid of women with endometriosis. PGE2 is produced by ectopic endometriotic cells themselves. The main prostaglandin product of the COX pathway, prostaglandin E2, acts posttranscriptionally, stabilizing COX2 transcripts in turn increasing the levels of COX2 enzyme activity promoting an inflammatory environment. The enhanced synthesis of prostaglandins due to upregulated COX2 via this feedback amplification loop mediates the inflammatory and pain responses and disease progression. COX2 enzyme has been found in ectopic endometriosis lesions [1]. There has been reported overexpression of COX2 as seen by immunostaining in endometriomas in comparison with peritoneal implants or rectovaginal modules [23]. Elevated levels of prostaglandin E increases VEGF, an angiogenic factor which in turn stimulates COX2 expression creating a positive feedback loop in favor of higher concentrations of PGE and VEGF [22]. New blood vessels form from preexisting capillaries with ongoing proteolytic degradation of extracellular matrix and simultaneous endothelial cell proliferation, migration, extension of endothelial cells and adherence to ECM, remodeling of the ECM, and formation of new lumen. This subperitoneal vascular network facilitates maintenance of endometriotic lesions. Via the COX pathway and IL-1, prostaglandins increase, increasing VEGF production inducing a positive feedback loop, with increased prostaglandins inducing increased aromatase leading to increased estrogen. Estrogen-mediated signaling in turn can increase apoptosis evasion via TNFα, also stimulating IL-1 [16].

VEGF is found in high levels in the peritoneal fluid as outlined above, and its activity is modulated by seven different angiogenesis-associated microRNAs that are involved in promoting vascular development. Its production and receptors are regulated directly by estrogen and progesterone. VEGF also functions to promote growth of nerve fibers [52]. The angiogenic factor Ang-2 is released when endothelial cells are activated via VEGF, bFGF, or TNFα. This destabilizes endothelium-allowed induction of angiogenesis by VEGF.

Immune Surveillance Evasion by Ectopic Endometrial Tissue

The ectopic endometrial tissue evades antibody and cell-mediated immune surveillance, and this altered immune response is a key factor in evasion of apoptosis. Macrophages present in the peritoneal cavity phagocytize and secrete cytokines in the normal setting. They represent 85% of the cells in peritoneal fluid. Their function is regulated by MMPs. There is a decrease in TIMPs, specifically TIMP-1. The dysregulation of endometrial MMPs synthesis and secretion alters macrophage

recruitment and facilitates cell invasion [13]. As an example, the steroid receptor coactivator-1 (SRC-1) has an isoform generated by MMP-9 that is highly elevated in endometriotic tissue and prevents TNFα-mediated apoptosis sustaining the endometrial ectopic tissue [15]. Epithelial-to-mesenchymal transition continues with invasion, eventual scarring, and symptomatic disease.

In endometriosis patients, peritoneal macrophages are increased and activated. Activated macrophages secrete TNFα, promoting further production of inflammatory cytokines [12]. Cytokines in turn activate T and B cells. IL-1 activates T lymphocytes and enhances B-lymphocyte proliferation. There is impaired cell-mediated immunity with altered macrophage capacity despite their increased numbers to induce cytolysis of ectopic endometrial cells [12, 13]. Phagocytosis of endometriotic cells by peritoneal macrophages is inhibited by prostaglandin E2 which is increased in endometriosis.

Increased expression of anti-apoptotic gene Bcl-2 in endometriotic tissue impairs cell apoptosis, reducing the percentage of menstruated cells undergoing programmed death. Ectopic endometrial cells are generally less differentiated than eutopic endometrial cells and are less likely to undergo apoptosis. There is also impairment of apoptosis of peritoneal macrophages, and despite their larger numbers, their cytotoxicity is reduced. Elevated TNFα in patients with endometriosis also contributes to resistance to apoptosis.

There is resistance to NK cell cytotoxicity by ectopic endometrial tissue with a decrease in both the number of NK cells and their function with altered cytokine secretion by NK cells [13]. This leads to altered T- and B-lymphocyte cell activation and defective autoantigen presentation by macrophages to T cells. T lymphocytes are significantly reduced in the peritoneal fluid of women with endometriosis [12]. T lymphocytes display reduced cytotoxicity. There appears to be increased B-cell activity. In Japanese women, a positive association with HLA-B7 allele and endometriosis was noted [2].

Overall, evasion of immune surveillance, activation of pro-inflammatory pathways, increased invasion by altered ectopic endometrium, and angiogenesis via multiple altered cytokines along with epigenetic modulation lead to progression of endometriotic lesions.

Advances in Medical Treatment

Adolescents experience the symptoms of endometriosis earlier in life, and they require maximal combined medical and surgical treatment via excision in order to minimize repeat surgical intervention. Medical management presently is aimed at suppression of ovarian estradiol production decreasing the stimulus for endometriotic growth and proliferation and inducing atrophy and/or decidualization. This is achieved by continuous rather than cyclical oral contraceptives with combination estrogen-progesterone, contraceptive patch, or vaginal ring [11, 21]. There is controversy as to whether hormonal suppression prevents recurrence or disease

progression [4, 7]. Intrauterine device with progestins has also been shown to be effective [7, 11, 14]. Progestins have been shown to suppress IL-8, TNFα, and NFκβ activation and inhibit MMPs and angiogenesis. Progestin continuous use for 6 months to treat endometriosis is another option. Concomitant use of NSAIDs remains a mainstay with inhibition of the cyclooxygenase enzyme pathway decreasing prostaglandin production decreasing pelvic pain.

Nezhat et al. evaluated the effectiveness of various oral contraceptives in treating unilateral or bilateral, presumed functional, ovarian cysts in women with histories of endometriosis. There was no significant difference between hormonal treatment with two differing doses of oral contraceptives and danazol versus expectant management. Of the 54 women studied, 19 underwent laparoscopy [60].

Gonadotropin-releasing hormone agonist (GnRH) use, although very effective with resolution of active disease and resolution of pain, is not an option for adolescents given the effect on final bone density formation [21]. It is a possible option with known endometriosis refractory to all other medical therapies. GnRH antagonist via a dose-dependent receptor blockade has shown a decrease in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia. It is not indicated for adolescents.

Suppression of ERα and ERβ activity via selective estrogen receptor modulators (SERMs) is another line of inquiry. The use of selective progesterone receptor modulators (SPRMs) with mixed agonist-antagonist properties suppressing ovulation and endometrial bleeding along with antiproliferative effects on the endometrium has been shown to be effective in inducing amenorrhea and decreasing pain [14].

Aromatase inhibitors (AIs) reducing estrogen biosynthesis represent another avenue, they are not FDA approved, and very high dosages are required suggesting they may be more effective as an adjuvant to suppress the rise in endogenous gonadotropins with GnRH agonist use. Combining aromatase inhibitors with add back progestin or oral contraceptives is another option. It has been shown to successfully decrease pain and amount of visible endometriosis [47]. Side effects with AIs are vasomotor symptoms, bleeding, joint pain, diminished libido, weight gain, sleep disturbance, bone loss, and lipid profile changes. It is not indicated for adolescents.

New approaches utilizing an understanding of molecular mechanisms can include targeting steroidogenesis as SF-1 is elevated in endometriotic cells, and this could include the use of statins. Statins via competitive inhibition of HMG-CoA reductase regulating the mevalonate pathway affect signal transduction steps, reducing expression of integrins; reduce oxidative stress, inhibiting MMPs; and at higher doses, inhibit angiogenesis, may affect apoptosis, and have anti-inflammatory and immunomodulatory properties. The potential to affect estrogen production via SF-1 needs investigation. The main risk is rhabdomyolysis and potential risk for teratogenicity in reproductive age women.

The synthesis of small molecule inhibitors including potential DNMT-specific inhibitors to modulate nuclear receptor gene response is another possibility. Kinase inhibitors since it has been shown that some kinase pathways are overactive in endometriosis represent another future course of inquiry, along with angiogenesis inhibitors. TNFα inhibitor pentoxifylline in a small RCT of 34 women showed a decrease

in visual analogue pain scores compared to placebo. A second RCT with 104 women only addressed fertility benefits.

Botanicals such as the Chinese multi-herb Yiweining [25], which decreases cytokine levels and expression of COX2 and curcuma which decreases cytokines and angiogenic factors [1] have to be considered. Botanicals under investigation include Chinese angelica, cinnamon, peach kernel, red sage root, corydalis, frankincense, myrrh, persica, prunella vulgaris, red peony, and white peony [25, 26]. Acupuncture is another modality; however, one small RCT with 18 patients demonstrated no difference between the two groups.

Conclusion

Endometriosis is an estrogen-dependent and progesterone-resistant pro-inflammatory hormonal chronic disease with protean manifestations, characterized by early onset in adolescence with a significant delay in diagnosis presenting with cyclic and acyclic pelvic pain. Over the last two decades, there has been an increasing understanding of the stepwise development of ectopic endometrial lesions in the pelvic cavity, an appreciation of the genetic and epigenetic processes affecting pathogenesis, and progress in understanding the cellular and molecular mechanisms underlying disease development. This provides an opportunity for earlier diagnosis and new treatment approaches focused on each aspect of the pathogenesis of the disease, from adhesion to invasion, to proliferation, to angiogenesis along with altered/impaired cellular immunity and altered apoptosis. Hormonal treatments remain a mainstay, and while there are many possibilities on the horizon, there remains an urgent need for a wider variety of medical treatment modalities.

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Chapter 6
The Genetic-Epigenetic Pathophysiology of Endometriosis: A Surgeon's View

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Introduction

In the absence of a clear understanding of the pathophysiology, endometriosis remains a poorly understood disease. A major problem is the absence of an animal model with enough similarity to the human myometrium, junctional zone (JZ), endometrium, placentation, and pregnancy disorders as preeclampsia. Prevention, diagnosis, and therapy are based on observational medicine and clinical experience. Without experimentation and without understanding the pathophysiology, our views on endometriosis are limited to clinical observations, histology, and biochemical investigations of endometriotic tissues.

The history of our understanding of the pathophysiology of endometriosis will be reviewed together with the recent genetic-epigenetic theory [1]. In order to understand these concepts on endometriosis, it is important to realize how our knowledge varied over time.

The History of Endometriosis

The early history of endometriosis, discussed at length in Chap. 2, is linked to the development of microscopy and histology. Only in the mid-nineteenth century, compound microscopes had acquired sufficient magnification, which together with tissue fixation and embedding techniques permitted the study of histologic structures. Modern histology started only at the end of the century after the development of a microtome. Rokitanski [2] is often credited with the first description of endometrium-like tissue in 1860. However, he (Fig. 6.1) described endometrial


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Fig. 6.1 The original article of Rokitansky

polyps and an ovarian cancer with endometrium-like cells. Descriptions of what today would be called deep endometriosis were made at the end of the nineteenth [3–5] and during the early twentieth [6–10] century. Slightly later, cystic ovarian endometriosis was described by Sampson [11, 12] who coined the name "endometriosis" [13, 14] and proposed the retrograde menstruation and implantation theory [11]. Over the next 50 years, numerous reports described "endometrium like tissue outside the uterus" found in all kind of surgery specimens. Aleady in 1960 [15], it was realized that endometriosis was a frequent finding in women undergoing surgery even after menopause.

Only after the introduction of diagnostic laparoscopy it was realized that black-puckered, "powder burn," superficial peritoneal lesions in sclerotic areas, later called typical lesions, were very frequent in women with pain and/or infertility. When in 1980 [16, 17] we realized that retrograde menstruation occurred almost systematically in all women, the search for early lesions after implantation started. Although occasionally described before [12, 18–22], the high prevalence of subtle lesions [23, 24] was only realized after 1986 [25]. Also, microscopic endometriosis [26, 27] turned out to be a frequent finding even in normal-looking peritoneum [28] and much later in lymphoid glands [29, 30] and in the bowel at distance from deep endometriosis [31]. With the introduction of transvaginal ultrasound, cystic ovarian endometriosis became a frequent finding. With the introduction of excisional laparoscopic surgery, some endometriosis lesions were found to infiltrate deeper under the peritoneal surface [32], and deep endometriosis became recognized as a frequent entity of endometriosis associated with severe pain, invasion into the muscle of the bowel wall, occasional nerve invasion [33], and a neurotropic effect [34, 35].

The Definition of Endometriosis and the Natural History

From the very beginning till today, the definition of endometriosis has been "endometrium like glands and stroma outside the uterus" diagnosed on histologic slides after routine staining. It is surprising that other staining techniques and histochemistry did not add to the diagnosis of endometriosis. Histology after routine staining thus remained the gold standard. A consequence of this definition is that all observations not fitting this histological definition are not recognized as endometriosis. This comprises Müllerianosis [36], stromatosis [37], and eventual atypical or precursor lesions. Also, vascularization and fibrosis are not included in the diagnosis.

The histology of endometriosis lesions seems well established. Subtle lesions have active glands and stroma, and typical lesions are generally burnt out. The endometrial component of cystic ovarian endometriosis varies from hemosiderin-laden macrophages only to inactive endometrial glands and stroma to occasional proliferative endometrium-like tissue. Deep endometriosis consists of fibro-muscular tissue with sparse glands and stroma which can be active in the deeper parts. It is important to realize that histology does not permit a clear distinction between typical and deep endometriosis. The distinction is surgical.

That larger cystic ovarian endometriosis and larger deep endometriosis lesions were a clinical pathology requiring surgery, was recognized from the beginning. However, it is much less clear whether all microscopic, subtle, typical, smaller cystic, and deep endometriosis lesions are a clinical pathology. This is not surprising since histological diagnosis requires excision.

For the same reason, the natural history of the disease is poorly known, and the concept that endometriosis is a progressive disease, although logic, is poorly documented [38]. Regression of smaller (subtle) lesions is common [39]. Rectovaginal deep endometriosis lesions without pain do not grow rapidly [40]. Also, the concept that endometriosis is a recurrent disease is mainly based on the frequently observed retrograde menstruation and the concept of implantation [41]. The available data do not permit to distinguish between recurrence because of incomplete surgery and the formation of new lesions. Moreover, studies rather describe recurrence of symptoms than recurrence of lesions [42]. Recurrence rates of cystic ovarian endometriosis following stripping are less than 10% within 6 months [43, 44] but vary with the surgeon [45] and with the technique used. Recurrence rates of deep endometriosis lesions after excision are rare (personal observations and [42]). The recurrence rates of typical lesions and subtle lesions are believed to be higher although the data are limited.

Observations and Associated Pathologies

Endometriosis occasionally occurs in women without an endometrium [46, 47] and in men [48, 49]. The epidemiology is unclear since diagnosis often requires a laparoscopy and since recognition varies with the expertise of the surgeon. This limits the information of hospital-based discharge records [50]. Subtle endometriosis lesions decrease with age, whereas typical, cystic, and deep lesions increase with age [51]. Clinical observation suggests that the prevalence and severity of deep endometriosis are increasing [40].

Endometriosis is *associated with pain and infertility* (Table 6.1). However, it is unclear whether microscopic and subtle endometriosis [31] commonly cause pain or infertility given the high prevalence in women with infertility with no pain [51]. Typical endometriosis is estimated to cause minor pain in 50% of women. Half of them are pain-free as estimated in women with infertility only [51]. However, analysis of pain is compromised as symptoms may not lead to a diagnosis in the 62% of women whose symptoms are only found on direct questioning [52, 53] or in those with no symptoms but with endometriosis found at tubal ligation [54]. Cystic ovarian endometriosis causes pain in over 80%, and deep endometriosis causes severe pain in the large majority of women [51]. Following surgical excision of endometriosis and after failed IVF and of deep endometriosis, 50% [55] and 30–50% [56] will conceive spontaneously, respectively. The mechanism of the associated infertility is unknown. That cystic ovarian endometriosis is a cause of infertility can be explained by the associated adhesions.

Table 6.1 Clinical observations in endometriosis

Clinical observations on endometriosis
1. Variable appearance (subtle-typical-cystic-deep)
2. Occurs also in women without endometrium and in men
3. An hereditary disease and predisposition
4. Natural history Most subtle lesions do not progress Most typical-cystic-deep lesions are not progressive after diagnosis Most typical-cystic-deep lesions are not recurrent after surgery
5. Epidemiology of endometriosis
6. An heterogeneous disease
7. Endometriosis is associated with Pain and infertility Adenomyosis Changes in plasma Changes in peritoneal fluid Changes in endometrium Changes in pregnancy outcome Pelvic infections Cancer risk Total body radiation and dioxin intake
The endometriosis lesion
8. Clonal
9. Altered biology: estrogen production – progesterone resistance, etc.

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Endometriosis is *associated with adenomyosis* [57]. Focal adenomyotic nodules are associated with deep endometriosis [58, 59]. Endometriosis is associated with *changes in plasma* as immunology [60–62], lymphocytes [63], prostaglandins [64], insulin-like growth factor I [65], and a decreased natural killer cell (NK) activity. *Changes in peritoneal fluid* are the luteinized unruptured follicle syndrome, with much lower concentrations of estrogens and progesterone after ovulation [66]; the low-grade inflammation with a high number of activated macrophages [67] and changes in cytokines [68, 69]; growth factors, acylcarnitines, phosphatidylcholines, and sphingomyelins [70]; vascular epithelial growth factor [71, 72]; and other angiogenic factors [73, 74] especially of the TGFb superfamily [75]; and increased concentrations of CA125 and of glycodelins [76]. Several hundred minor biochemical *changes in the endometrium* have been described [77, 78]. *Contractility of the uterus* is modified in women with deep endometriosis or adenomyosis [79]. *Changes in pregnancy,* mainly associated with cystic ovarian and deep endometriosis [80], and with adenomyosis [81], are abnormal placentation, insufficient physiologic changes in the spiral arteries, an increased risk of preterm birth, small for gestational age (SGA) babies, and preeclampsia [80]. Endometriosis is associated with a higher risk of vaginal [82], uterine [83], and pelvic *infections* [84]. Endometriosis seems associated with a higher *risk of cancer* [85, 86] [87], although the association with ovarian cancer remains debated [88] and with *dioxin* [89, 90] and *total body radiation* [91, 92].

Endometriosis is *a hereditary disease* with a 6–9% [93] and a 15% [94] increased risk of developing endometriosis in first-degree relatives of women with mild and severe endometriosis, respectively. This, together with the familial clustering in humans [95] and primates [96] and the prevalence [97] and the age of onset [98] in twin sisters, permitted the conclusion that hereditary factors accounted for 50% of endometriosis [99, 100]. The molecular mechanisms involved are not yet understood [101]. Genome-wide scanning and linkage analysis did not identify the genes involved [102]. The two loci found by linkage analysis have low LOD (logarithm of odds) scores. The 10 [103] or 15 [104] loci found by genome-wide association studies in women with severe endometriosis were located in DNA sequences regulating target genes [105]. A meta-analysis found 5 loci regulating sex steroid hormone pathways, 5 secondary signals, and 19 single nucleotide polymorphisms [106]. The investigation of specific hereditary predisposition factors as detoxication enzymes was negative [107].

Endometriosis Lesions Are Clonal with an Altered Biology Clonality was demonstrated for typical [108], deep [109], and cystic ovarian [110–112] endometriosis. Multiple lesions in one woman derive from different progenitor cells [108]. Investigation of larger endometriosis lesions [113–115] found aromatase activity [113] and progesterone resistance [114–116] together with numerous other biochemical changes [117–123]. These changes are increasingly viewed as a consequence of genetic or epigenetic polymorphism [113, 124]. Other epigenetic changes [125–127] comprise methylation, demethylation of DNA, and modifications in histone code [125, 128].

The Theories of Pathophysiology

A theory remains valid until disproven by new observations.

The Sampson Theory and the Metaplasia Theory

When formulated 100 years ago, the implantation theory [11, 13, 18] after retrograde menstruation or after lymphatic or blood embolism was logic. This theory became even more attractive when retrograde menstruation was found to be rather the rule than the exception. Retrograde menstruation contains living cells [129] with implantation and growth potential of cells [130, 131] and tissue blocks [131] as observed directy by the implantation of endometrial fragments in a neonate [132]. That pelvic endometriosis is more frequently found on the left side of the pelvis [133] and on the right side of the diaphragm seems consistent with gravity and with the clockwise circulation of peritoneal fluid. Also, the frequent finding of subtle lesions seemed consistent with this hypothesis. If considered like endometrium, it is

logical that endometriosis is estrogen and progesterone responsive, that active endometriosis does not occur after menopause, that endometriosis symptoms disappear during pregnancy, and that ovarian suppression is an effective medical therapy. The associated changes were explained as consequences of the endometriosis developing in an abnormal location. Neonatal menstruation [134–136], occurring especially in postmature and SGA babies, might explain premenarcheal and severe adolescent [137] endometriosis.

A weakness of the hypothesis was that it could not explain why subtle lesions developed into endometriosis in some women only, and why some developed into typical, cystic, or deep endometriosis. The hereditary character of endometriosis is difficult to explain, but not incompatible.

The implantation theory does not explain the clonal aspect of endometriosis lesions, many of the biochemical changes in the endometriosis tissue, and the rare active deep endometriosis more than 10 years after menopause [138]. Moreover, it is incompatible with the observation of endometriosis in women without an endometrium and in men.

The occurrence of endometriosis in women with a Rokitansky syndrome was realized already a few years after Sampson formulated his implantation theory, and therefore, the metaplasia theory was formulated [47]. After this, both theories which were otherwise similar survived side by side. The metaplasia theory was recently updated with a development from stem cells, either peritoneal [139–143] or uterine [144, 145], from bone marrow cells [140, 146–149], pale cells [150, 151], and embryonic remnants [152]. These concepts find support in the frequent mesothelial-mesenchymal transitions (MMT) with a role of platelets [153] and in the role of bone marrow cells in peritoneal repair [154].

Another variant was the archimetra theory emphasizing enhanced or abnormal uterine contractions as a cause of trauma in the endometrial-myometrial JZ [150] and of endometrial cell seeding [155].

The Endometriotic Disease and the Genetic-Epigenetic Theory

The endometriotic disease theory postulated in 1999 [156] that subtle lesions consisted of normal endometrial cells, occurring intermittently in all women [157], and that a genomic incident was required before these cells developed into typical, cystic, or deep endometriosis. In order to emphasize this difference between normal and abnormal cells, it was suggested to call them endometriosis and endometriotic disease.

The genetic-epigenetic theory (Fig. 6.2) updates the endometriotic disease theory [1]. All humans are born with a specific set of minor genetic and epigenetic (G-E) incidents transmitted by the parents or acquired in utero (Fig. 6.3). This can explain the heredity predisposition of endometriosis and most endometriosis-associated changes in plasma, immunology, peritoneal fluid, and even the infertility. They can also explain changes in uterine mobility and the changes during

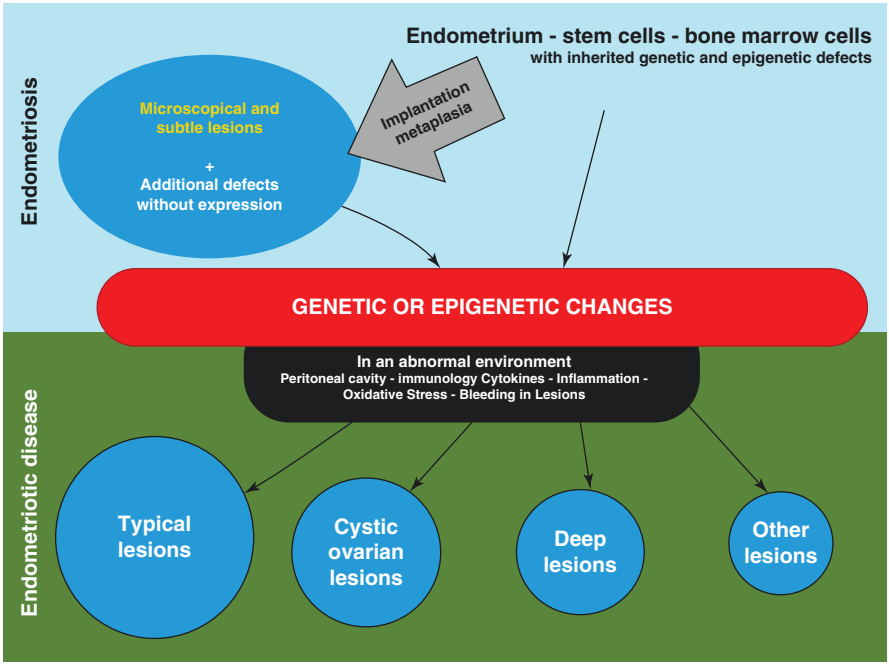

Fig. 6.2 The genetic-epigenetic theory. The original cell can be an endometrial cell or a stem cell or a bone marrow cell with their inherited genetic and epigenetic defects. These defects, together with additional acquired defects without expression, constitute the predisposition. Following implantation or metaplasia, defined as stable and transmittable changes, subtle and microscopic lesions occur. Additional genetic or epigenetic changes are required for these cells to change behavior and to progress into typical, cystic, deep, or other lesions. (Reproduced with permission from [1])

pregnancy since these effects are not corrected after surgery for deep endometriosis [158]. That the decreased NK activity in plasma remains low after surgical excision of deep endometriosis suggests that the NK cell defect is not a consequence of endometriosis [159].

During life, additional G-E incidents occur, either as occasional incidents during cell cleavage or as a consequence of environmental toxins as dioxin or radiation with known genomic and epigenetic [160] effects. Most incidents will be repaired, or the cell will become apoptotic. If the cell survives, they can accumulate a series of incidents over time. Most incidents will remain invisible since most of the molecular biological pathways are redundant [161]. Only when cumulative G-E incidents exceed a certain threshold and/or when the external stressors require more metabolic activity than permitted by the cumulative incidents abnormalities become visible, and these cells can start their development into endometriosis. This explains the clonal aspect of endometriosis lesions. This also explains the large variability within endometriosis lesions with little or high aromatase activity and with progesterone resistance varying from very severe to nonexistent.

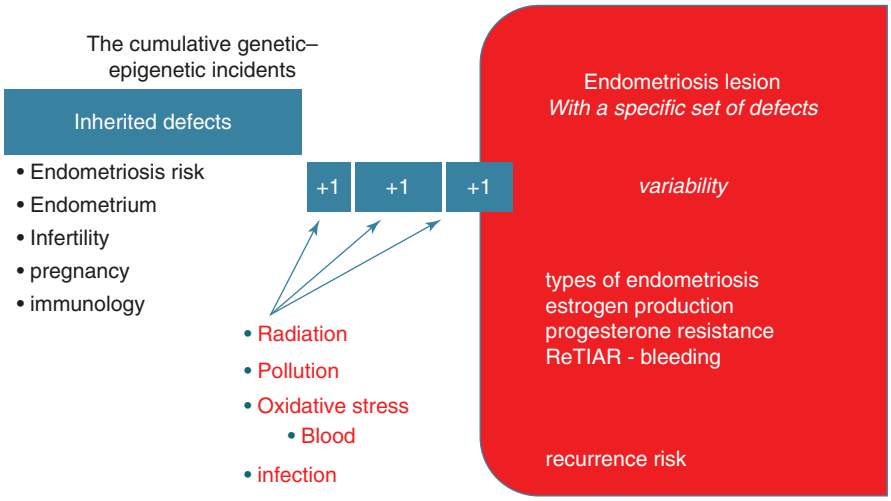

Fig. 6.3 The cumulative genetic-epigenetic incidents. Some endometriosis-associated observations can be explained by inherited defects. During life, additional defects occur because of radiation, pollution, or oxidative stress. After transcending a threshold, caused by the cumulative defects and/or an increased cellular stress and/or the abnormal environment, these cells start their growth to form endometriotic lesions which are variable macroscopically, biochemically, and clinically

The original cell is less important and can be endometrium after neonatal or adult retrograde menstruation, peritoneal or endometrial stem cells, peritoneal cells after mesenchymal-mesothelial transformation, or even bone marrow cells. What is important is that these cells are genetical-epigenetically "normal" cells which can form transient subtle lesions after implantation.

Molecular biology already has identified many potential G-E alterations which might be involved in the development of endometriosis. A comprehensive understanding of changes, however, remains hampered by the redundancy and complexity of pathways.

Our Actual Understanding of the Development of Endometriosis Lesions

The endometrium is one of the fastest growing tissue in the human body with a special relationship with the junctional zone as evidenced during placentation. Any acquired abnormality of the functionalis of the endometrium will be eliminated during menstruation. This mechanism is considered to explain the increased incidence of endometrial cancer immediately after menopause. Outside the uterus, however, such as in the peritoneal cavity these cells are no longer eliminated.

An endometrial cell or any other cell in the peritoneal cavity develops in the specific environment of the peritoneal cavity with different concentrations of

proteins and steroid hormones, with a different immunology and microbiome and an increased oxidative stress. The latter is increased by the amount of retrograde menstruation [162]. Both the microbiome, from ascending infection and from transmural migration from the intestine [82, 84, 163], and the oxidative stress have the potential to cause G-E incidents, which explains that endometriosis develops mainly in the pelvis and the relationship with a more abundant retrograde menstruation [164] causing more oxidative stress and more retraction of peritoneal mesothelial cells, thus facilitating the implantation of endometrial cells [165, 166].

The further growth of the endometriosis lesions will vary with the specific set of incidents in the lesion, such as aromatase activity and progesterone resistance, and with the environment. What is important is that also the environment such as the low-grade inflammation in the peritoneal cavity, the angiogenic factors, and the activated macrophages with their secretion products will vary with the set of incidents transmitted at birth and acquired during life. In addition, the monthly bleeding in the lesion during menstruation constitutes a specific oxidative stress which risks to cause additional G-E incidents. It, moreover, is a repetitive tissue injury that needs to be repaired [167].

Growth of typical and deep endometriosis lesions seem to be self-limiting. After a period of growth, most lesions seem to stop growing which is the case for most lesions at diagnosis. Some rare deep and cystic lesions; however, they seem very active during surgery and seem to continue growth.

The role of the intraovarian concentrations of steroid hormones in the development of cystic ovarian endometriosis must play a role, but this has not yet been adequately investigated.

The G-E theory is compatible with all observations on endometriosis today. That many of the molecular biological alterations described in endometriosis lesions are increasingly viewed as the result of genetic and epigenetic incidents lends further support to the G-E hypothesis. However, it should be stressed that the implantation and growth of endometriosis lesions and the associated inflammatory reaction could also explain some of the associated observations, such as the increased nerve density [168, 169]. Another example is the high glycodelin concentrations in peritoneal fluid which may protect early lesions from NK cell attack [170, 171] and thus could facilitate survival.

Clinical Implications of the G-E Pathophysiology

The Relationship with Ovarian Cancer

The G-E theory is a similar mechanism as those leading to cancer. Although not conclusively proven, the repetitively suggested association of cystic ovarian endometriosis with ovarian cancer is not that surprising, since endometriosis already has a series of incidents such as cancer driver mutations [123]. In addition, the emerging

association of endometriosis with pelvic infection and the demonstrated decrease in ovarian cancer after tubal ligation might suggest similar mechanisms.

Prevention of Endometriosis Onset, Recurrences, and Growth

The G-E theory suggests that a reduction of oxidative stress in the peritoneal cavity might become a prevention of endometriosis onset and recurrences. This could be achieved by oral contraception given continuously. Not yet explored are therapies as progesterone antagonists in lower doses. Also, the once popular tubal ligation, which can be performed as a 5-minute procedure under local anesthesia, might be considered when conception is no longer considered.

A reduction of the overall oxidative stress by fruit, vegetables, and other antioxidants might be considered. Understanding the relationship between food intake and the intestinal microbiome and of transmural migration of pathogens from the bowel as Shigella opens new concepts of endometriosis and food intake.

These concepts of prevention of growth and recurrences are especially important for younger women.

Treatment of Endometriosis Lesions

Typical, cystic, and deep endometriosis are three different diseases harboring a different set of G-E incidents. In addition, this set differs in each clonal lesion, which explains the marked heterogeneity in endometriosis lesions. Most deep endometriosis lesions are painful, and some not. Some typical lesions cause pain, and some not. Some deep endometriosis lesions are progressive, and most not.

Surgery is the treatment of choice if endometriosis is considered a benign tumor. However, radicality of surgery is less clear. It is conceivable that the fibrotic rim around a deep endometriosis lesion and the growing cell columns are reactive and metaplastic changes induced by the central core of tumor. This is compatible with the observation that recurrence rates of deep endometriosis are not remarkably different following conservative excision leaving a rim of fibrosis, aggressive conservative excision, and a small or a large bowel resection. If confirmed, this would be a major argument that radicality should be tailored.

Most important for medical therapy is the individualization of therapy because of the heterogeneity of endometriosis lesions. It should be realized that an analysis with statistics describing means and standard deviations will not pick up that a therapy might stimulate instead of decrease endometriosis lesions even if stimulation occurs in 20% of patients (Fig. 6.4). For this reason, we advocate to reconsider treatment if the patient does not respond sufficiently within a few months. This heterogeneity should also be reflected in the analysis of data where individual responses should be evaluated in order to detect hidden subgroups.

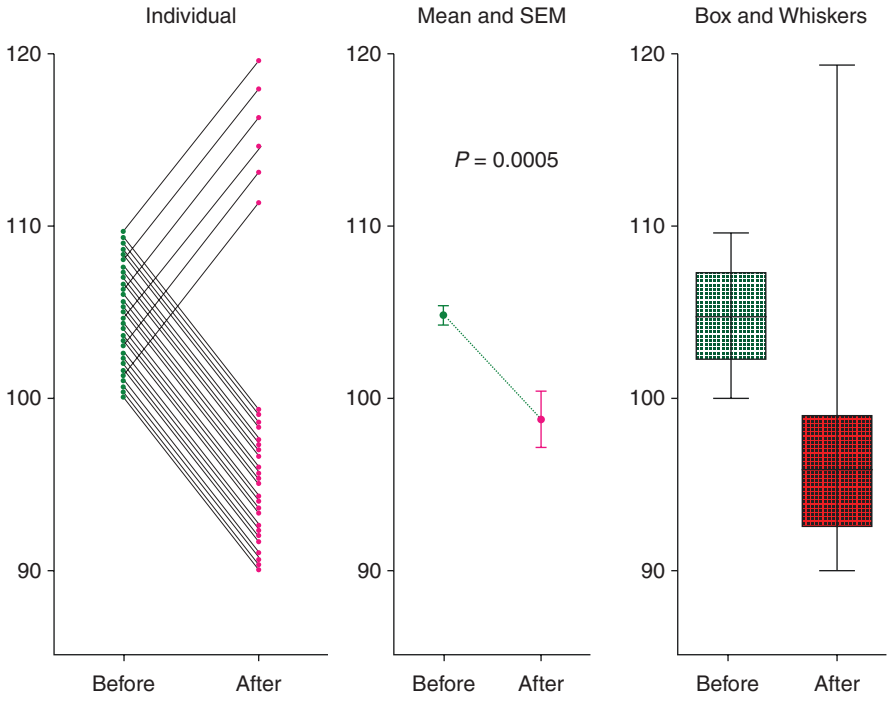

Fig. 6.4 A data set with 24 women decreasing and six increasing pain by 10% after treatment. Heterogeneity of response is obvious when the individual data are plotted but hidden when only means and SEM are given. The variability in response is suggested by box and whiskers plots. Students' t-test results in $P = 0.0005$. (Reproduced with permission from FVVO)

Discussion and Conclusions

Activation and repression of DNA transcription and the subsequent translation are complex processes with complex regulatory mechanisms. Epigenetics are stable transmissible changes in DNA expression without DNA changes [172]. This, however, permits different definitions [173]. The NIH Epigenomics Mapping Consortium [174] uses epigenetics to indicate changes in gene expression; others use it to refer to transgenerational effects and inherited expression [175]. Epigenetics is used for both reversible and for stable changes that are transmitted after cleavage. When transmitted at birth, they are called the epigenetic trait [176].

The meaning of many words used in endometriosis did change over time when new clinical and molecular-biological observations were added to the initial clinical, macroscopic, and microscopic descriptions. Metaplasia was introduced as a descriptive histological observation, without the concepts of stable, reversible, and transmissible changes. We know from stem cell research that changes during cellular differentiation can be stable and transmitted, although reversible. It is unclear whether "metaplastic" changes preceding the development of cancer are reversible

or whether they signal some stable changes which increase the risk that another incident will start the development of a malignant tumor. Metaplasia, thus, is used to indicate the (reversible) expression of environmental stress [177] and also to indicate the expression of stable genetic or epigenetic damage. If metaplasia is defined as metaplastic changes without permanent and transmissible genetic or epigenetic changes, the resulting endometriosis cells are genetically and epigenetically similar to endometrium. If, on the contrary, metaplasia indicates stable and transmissible genetic or epigenetic changes, this comes close to the G-E theory.

The G-E theory is also important for our views on nonhuman models of induced endometriosis, in both primates and rodents. These models remain valid to study the effect of abnormal environments on (normal) endometrium. Transplantation of human endometriosis into SCID/nude mice could be a model to study the development of (abnormal) endometriotic tissue in a normal or controlled environment.

In conclusion, the G-E theory of endometriosis explains endometriosis as the consequence of a cumulative set of genetic and epigenetic incidents in endometrial, stem, or other cells developing in an abnormal environment with already a specific set of G-E incidents acquired at birth. Prevention of endometriosis, thus, should focus on the prevention of new incidents through reduction of oxidative stress by retrograde menstruation and by understanding the peritoneal microbiome and the relationship with food intake and a reduction in environmental pollutants. Medical therapy should take into account the heterogeneity of lesions, and the radicality of surgery might be reconsidered.

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Conflicts of Interest None of the authors have a conflict of interest to declare.

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Chapter 7
Optimal Management of Endometriosis and Pain

Camran Nezhat, Nataliya Vang, Pedro P. Tanaka, and Ceana H. Nezhat

The pathophysiology of endometriosis-associated pain involves inflammatory and hormonal alterations and changes in brain signaling pathways. Although medical treatment can provide temporary relief, most patients can achieve long-term sustained pain relief when it is combined with surgical intervention. Owing to its

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complexity, there is an ongoing debate about how to optimally manage endometriosis-associated pain. We believe optimal management for this condition requires (1) possible egg preservation in affected young patients with and without endometriomas, (2) preoperative medical suppression to inhibit ovulation and to avoid removal of functional cysts that might look like endometriomas, and (3) postoperative hormonal suppression to decrease recurrence, but this treatment should be modified according to disease severity, symptoms, and fertility goals.

Endometriosis is a hormone-dependent progressive inflammatory disorder that develops when endometrial-like tissue is formed outside of the uterine cavity. Chronic pain, infertility, and organ dysfunction are the key clinical features [1, 2]. Approximately 5–10 million reproductive-aged women in the United States suffer from endometriosis—the great imposter [2]. Because of its complex nature, it can take 6–10 years to diagnose endometriosis, and its symptomatology varies tremendously [1, 2]. Most patients experience cyclic pelvic pain with menses, but some experience symptoms of noncyclic pelvic pain, such as dyspareunia, dyschezia, and dysuria. Characteristically, pain severity does not correlate with the amount of endometrial tissue formed. Many patients present only with unexplained infertility. As Giudice states, "infertility results from the toxic effects of the inflammatory process on gametes and embryos, compromised fimbrial function, and eutopic endometrium that is resistant to the action of progesterone and is inhospitable to embryonic implantation." [3]. However, endometriosis can produce symptoms that mimic other diseases, including irritable bowel syndrome; interstitial cystitis; vascular, musculoskeletal, neurologic, and psychological diseases; obesity; anorexia; thyroid dysfunction; autoimmune disorders; and heart disease.

The etiology of endometriosis is still not fully understood, but estrogen plays a major role in its pathogenesis. A commonly accepted theory that endometriosis is caused by retrograde menstruation was introduced in the seventeenth century by Ruysch, and this was later supported by Sampson [2]. In the early 1900s, Thomas Cullen recognized that endometriosis could invade pelvic nerves [2]. One theory is that endometrial-like tissue enters the peritoneal cavity through the fallopian tubes, and this ectopic tissue persists by establishing its own blood supply to ensure its survival and create a protective environment to prevent the immune system from clearing the ectopic tissue. In fact, the implant can attract inflammatory cells, which further potentiates its growth. Moreover, this ectopic endometrial-like tissue is biologically active outside of the uterus [3].

Endometriosis-Associated Pain

The pelvis is highly vascularized and enervated, which is why pain impulses from this region are processed and sent to the brain (Fig. 7.1) [4–6]. This, along with multiple other factors, contributes to the pain syndrome that is associated with

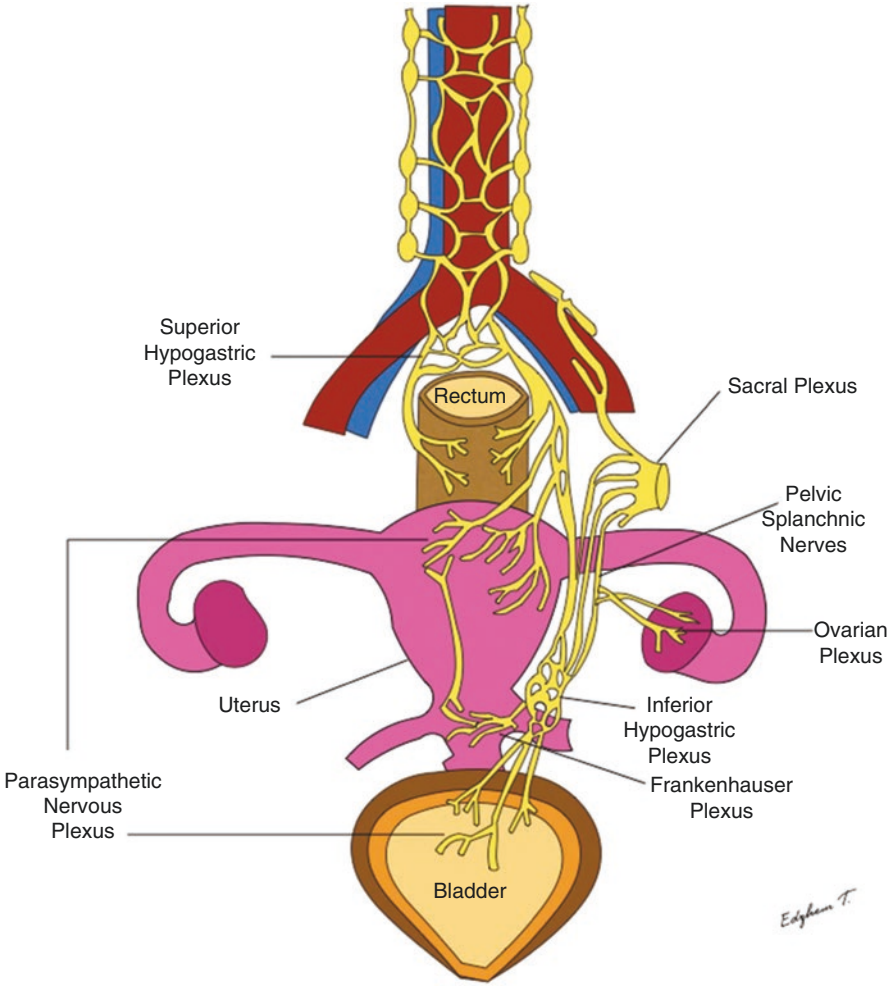

Fig. 7.1 Pelvic nerve supply. Superior hypogastric plexus, which contains sympathetic and sensory afferent fibers from the uterus, is an extension of the aortic plexus at the fifth lumbar vertebra. This plexus divides into right and left hypogastric nerves that join the pelvic splanchnic nerves from S2 to S4. Pain impulses from the uterus and cervix travel through afferent sympathetic nerves, which are found in the uterosacral ligaments and posterolateral pelvis. These coalesce in the midline as the superior hypogastric plexus and travel to the dorsal root ganglia of the spinal cord. These pain stimuli are then processed and sent to the brain. Illustration by Edzhem Tombash and Camran Nezhat. (Used with permission. Adapted by permission from Springer Nature: Nezhat et al. [6]. Copyright 2017. Macmillan Publishers Limited, part of Springer Nature. All rights reserved.) *Nezhat. Endometriosis and Pain. Obstet Gynecol 2019*

endometriosis. Peritoneal fluid in women with endometriosis contains high levels of nerve growth factors that promote neurogenesis, the ratio of sympathetic and sensory nerve fibers is significantly altered within endometriotic tissue, and the nerve density within endometriotic nodules is increased [7, 8]. Also, the cytokines and prostaglandins produced by mast cells and other inflammatory cells attracted to ectopic endometrial-like tissue can activate nerve fibers and can trigger nearby cells to release inflammatory molecules [5, 6, 8, 9].

Another source of pain is nerve fiber entrapment within endometriotic implants [4]. The cyclical sciatic pain, weakness, and sensory loss can all stem from endometriotic entrapment of the sciatic, femoral, or lumbosacral nerve roots [9]. There are numerous descriptions of sacral radiculopathy occurring in patients with endometriosis, and there are even descriptions of wheelchair-bound patients becoming fully ambulatory after treatment of infiltrative endometriosis [9].

Central sensitization is another mechanism that promotes endometriosis-associated pain. Patients become highly sensitive to subsequent painful stimuli because of endometriosis-induced neuroplastic changes in descending pathways that modulate pain perception [10]. In response to a subsequent insult (i.e., nephrolithiasis or peritoneal organ injury), women can experience pain from endometriosis as a result of inability to engage descending inhibition pathways [10].

Medical Management

Pain management should be individualized. The goal of medical therapy is to reduce pain by decreasing inflammation as well as ovarian and local hormone production (Table 7.1). Complete estrogen suppression may not be necessary to relieve endometriosis-associated pain [11]. Medical treatment is usually not curative but suppressive, and symptoms will often recur after therapy discontinuation. The recurrence rate of endometriosis is highly variable, ranging from 4 to 74 [2, 3].

Initial treatment is typically use of combined oral contraceptive pills, which are effective in decreasing pain as well as in preventing postoperative recurrence [12]. For those who cannot tolerate or have contraindications to estrogen, progestins such as medroxyprogesterone acetate, norethindrone acetate, or levonorgestrel are indicated. However, there are patients who have decreased receptor sensitivity as a result of aberrant gene expression in the eutopic endometrium that leads to progesterone resistance [13]. For those unable to tolerate oral medications, the levonorgestrel-releasing intrauterine system can reduce pain and recurrence [4, 14]. However, the levonorgestrel-releasing intrauterine system does not inhibit ovulation and the recurrence of endometriomas. For those patients for whom the previous options have failed, we recommend using a gonadotropin-releasing hormone (GnRH) agonist with add-back therapy to prevent bone loss and to ease side effects. Patients taking GnRH agonists for endometriosis may develop resistance because endometrial-like tissue expresses aromatase and produces its own estradiol.

Table 7.1 Medical treatment options for endometriosis-associated pain

Medication	Characteristics	Side effects
Combined OCPs	First line Oral, patch, and ring Continual use (skip 7-d placebo) Temporary relief and inexpensive Decreases pain by 52% Limited use in patients with migraines Continual use decreases recurrence of pain after surgical excision	Thrombotic risk, nausea, weight gain, breakthrough bleeding, depression, breast tenderness, headache, and amenorrhea
Progestins	Oral, depot injections, implant, and IUD Temporary relief and inexpensive Decreases severity of diarrhea, intestinal cramping, and passage of mucus in colorectal endometriosis	Weight gain Decreased libido Depression
	Decreases deep dyspareunia Develops resistance IUD insertion decreases pain after surgical treatment	Fluid retention
GnRH agonists	Second line, must have diagnostic workup before administration Depot injection and expensive temporary relief Limited use up to 1-y with add-back therapy improves pain scores 60–100% 53% recurrence of symptoms after 2 y	Changes lipid profile, depression, hot flushes, bone loss, and urogenital atrophy
Aromatase inhibitors	Not FDA approved Use for those for whom other therapies have failed Major side effects Limited duration	Hot flushes, myalgia, and arthralgia
GnRH antagonists	Oral administration, expensive Use limited to 6 mo Improves dyspareunia and dysmenorrhea	Mood changes, hot flushes, loss of libido, vaginal dryness, and mild decrease in axial bone density

OCP oral contraceptive pill, *IUD* intrauterine device, *GnRH* gonadotropin-releasing hormone, *FDA* US Food and Drug Administration

Our experience is mixed with GnRH antagonists, aromatase inhibitors, and bazedoxifene along with conjugated estrogens. Some patients obtain pain relief from these medications, but others discontinue them prematurely owing to high expectations of fast mitigation of symptoms.

Since use was legalized in California, tetrahydrocannabinol and cannabidiol, either separately or in combination, present an alternative option. Patients frequently prefer these compounds over opioids, and their use is associated with less nausea and constipation. The use of tetrahydrocannabinol or cannabidiol is especially

beneficial for managing postoperative pain, and their use does not have the addictive concerns associated with opioid use. We use an enhanced recovery after surgery protocol and highly discourage opioid use.

Acupuncture is another potentially useful adjunct in treating the pain. It has been proposed to work by activating descending inhibitory pain pathways while centrally deactivating pain signals. Acupuncture also increases the pain threshold and leads to production of neurohumoral factors such as dopamine, nitric oxide, noradrenaline, acetylcholine, and others [15]. In addition, it increases natural killer cells, thereby modifying immune function and decreasing estrogen production [15].

Pelvic physical therapy has been shown in a retrospective study to improve endometrial pain in 63% of patients after at least six sessions [4]. Deep pressure massage, stretching pelvic floor muscles, joint mobilization, foam rollers with breathing, and relaxation techniques are the integral elements.

Surgical Management

Surgery remains the mainstay in definitive diagnosis. High-definition video laparoscopy with or without robotic assistance is the standard initial approach. In our extensive experience, laparotomy is seldom necessary. Excellent illumination with enhanced video magnification enables better recognition of subtle lesions as well as the depth of infiltrative lesions. Depending on the patient's desire, location of lesion, availability of proper instrumentation, as well as the experience and skill of the surgeon, eradication of endometriosis can be achieved with surgical management techniques that include excision, vaporization, and ablation. The nonsurgical options discussed above can be used to supplement surgical treatment for long-term results [4].

The best surgical approach for the treatment of superficial endometriosis is controversial. A meta-analysis of randomized controlled trials involving 335 women demonstrated that excision of endometriosis was superior to coagulation in reducing dysmenorrhea, dyschezia, and chronic pelvic pain when evaluated at 12 months of follow-up [16]. Laser ablation with layer-by-layer vaporization of endometriosis was shown to be 65% effective in reducing pain, compared with the 22% reduction when diagnostic laparoscopy alone was performed [16].

Laparoscopic uterosacral nerve ablation to disrupt efferent nerve fibers has been tested. However, multiple large randomized controlled trials did not find it to be beneficial in reducing endometriosis-associated pain. Complications of subsequent uterine prolapse and intraoperative ureteral transection have been reported with this procedure [16]. In contrast, laparoscopic presacral neurectomy was 87% efficacious in reducing severe midline pelvic pain [2, 4–6]. We find this procedure especially effective in patients with mild or no endometriosis [17]. The adverse effects associated with presacral neurectomy are constipation and bladder and urinary symptoms [17]. We perform presacral neurectomy in only about 1% of our patients.

A prospective, multicenter cohort study of 981 women with varying degrees of disease showed significant postsurgical symptom improvement over 36 months in patients who underwent laparoscopic excision of endometriosis. The most notable improvement was seen in dysmenorrhea, with a 57% reduction in symptoms; chronic pelvic pain and dyspareunia were reduced by 30. Owing to recurrent pain, a second-look surgery was performed in 9% of patients, and histologically confirmed endometriosis recurrence was documented in 5%. Of these patients, 7% benefited from medical therapy [18].

Abbott et al. demonstrated significant pain relief (80%) after surgery compared with a placebo group (32%). They report progression of disease with second-look laparoscopy in 45, no change in 33, and improvement in 22% of patients. Twenty percent of cases were not responsive to surgery [18].

Several noninvasive diagnostic tests for endometriosis, such as BCL6 and endometrial function tests and blood and saliva tests, are becoming available. These tests are especially important for asymptomatic infertility patients and for younger patients for whom we recommend egg preservation if possible. We individualize management of ovarian endometriosis and endometriomas based on the patient's age, fertility desires, family history of ovarian cancer, and type of endometriomas [4]. For many infertility patients, restoration of anatomy along with methodical and meticulous treatment of endometriosis can lead to natural conception or increase in overall in vitro fertilization success [19]. The treatment of endometriosis needs to be thorough to be effective. We recommend preoperative medical suppression to inhibit ovulation and to avoid removal of functional cysts that might look like endometriomas and possibly decrease inflammation.

We prefer conservative treatment for lesions of the rectum and rectal bulb close to the anal verge with associated sympathetic and parasympathetic nerve involvement. This can be accomplished by shaving excision and disc resection rather than through segmental resection (Fig. 7.1) [5]. Injury to the neurovascular structures could lead to gastrointestinal and genitourinary (GU) complications such as severe constipation, urinary retention, and loss of bowel or bladder function (Fig. 7.1) [5, 6].

Untreated endometriosis of the GU system can have dire side effects, such as silent kidney loss [6]. Radical surgical management of problematic GU endometriosis may require segmental bladder resection, ureterolysis, ureteral resection and reanastomosis, and ureteroneocystostomy with or without psoas hitch (Fig. 7.1) [6].

For the perimenopausal patient who has completed childbearing but still desires conservative treatment, we recommend surgical treatment of endometriosis as well as endometrial ablation with salpingectomy to prevent future pregnancy and reduce the risk of ovarian and fallopian tube cancer. We also recommend postoperative medical therapy and long-term follow-up to monitor for recurrence. For patients who do not desire future fertility and have debilitating symptoms for which other therapies have failed, we discuss the risk/benefit ratio of a hysterectomy with bilateral salpingectomy as well as postoperative medical suppression to mitigate recurrence. We inform patients that ovarian conservation is not optimally effective owing to continued hormonal stimulation of microscopic endometriotic lesions. However,

in a young patient, bilateral salpingo-oophorectomy in addition to hysterectomy without hormone therapy may lead to early onset cardiovascular disease, osteoporosis, and urogenital atrophy. In patients with catamenial pneumothorax associated with thoracic endometriosis, we recommend bilateral salpingo-oophorectomy when they have completed childbearing and when risks of video thoracoscopy outweigh the benefits [4, 20]. Management of surgical menopause with estrogen alone can stimulate growth of endometriosis. Patients who have undergone hysterectomy with bilateral salpingo-oophorectomy with subsequent adjuvant combined estrogen and progesterone for endometriosis suppression were found to have a low risk (4%) of recurrence [20]. On the contrary, when progesterone is not used, the recurrence of endometriosis is 5–15 [2, 3].

If removal of the uterus is indicated, we favor a total hysterectomy over a supracervical approach. The rationale lies in the evidence of abnormally increased nerve density in the endometrial implants in the cervix. Up to one quarter of patients will undergo subsequent trachelectomy owing to pelvic pain or bleeding after hysterectomy. Tsafrir et al. [21] demonstrated that the most common pathologic diagnosis and indication for trachelectomy was endometriosis. In a retrospective review after supracervical hysterectomy, 18 of patients reported pelvic pain and 10% reported dyspareunia related to the remaining cervix. These patients ultimately underwent trachelectomy [22]. In a review of trachelectomy samples, higher cervical nerve fiber density was found in women for whom pelvic pain was the procedure indication compared with the control group who had nonpain indications [22]. Laparoscopic trachelectomy is indicated for endometriosis patients with persistent pelvic pain after supracervical hysterectomy [23].

Though deeply infiltrative endometriosis can invade the superior and inferior hypogastric plexus, as well as the sympathetic and parasympathetic nerve bundles, surgical injury can lead to even more devastating effects. We use the Tokyo method to preserve nerves supplying the bowel, bladder, and sexual organs. This nerve-sparing technique includes separation and ligation of the vascular portion of the cardinal ligament while preserving the branches of the pelvic splanchnic nerves (Fig. 7.1) [5, 6]. We have previously suggested leaving some rectal disease behind and opting for postoperative hormonal suppression. This decreases the risk of injuring the rectum or its neurovascular bundle, which would necessitate a permanent colostomy (Fig. 7.1) [5].

Surgical treatment of endometriosis can be challenging owing to its highly vascularized, deeply invasive nature. Endometriosis can distort the anatomy, leading to indistinct planes of dissection. To treat patients adequately, the surgeon must be comfortable dissecting the retroperitoneal spaces. From our experience, it is evident that hormonal suppression may decrease inflammation, allowing for less bloody dissection and optimization of lesion excision. We therefore recommend some form of temporary hormonal suppression before surgery for patients with advanced endometriosis [24].

Postoperatively, these patients will still need an individualized hormonal treatment plan to prevent microscopic or residual endometriosis from flourishing. Gonadotropin-releasing hormone agonists and progestins have been shown to

significantly reduce pain [14]. Postoperative hormone therapy should include both estrogen and progestogen because estrogen alone may stimulate growth of microscopic disease.

In summary, endometriosis is a lifelong disease that can affect almost every organ in the body. The hormonal imbalance and the proinflammatory milieu alter neuronal signaling systems, which can alter pain processing. An individualized approach is required for the initial pharmacologic plan, and this should be included in the perioperative treatment plan. Although rare, the risk of cancer arising from endometriosis warrants close monitoring [25]. The complex and multifactorial nature of endometriosis requires a multidisciplinary approach to treatment. A combination of medical, surgical, psychotherapeutic, and alternative treatments can improve quality of life for women who suffer from endometriosis. Currently available knowledge and advanced surgical techniques can be used to reduce the torment and suffering of those afflicted with endometriosis.

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Chapter 8
The Presence of Endometriosis in the Human Fetus

Pietro G. Signorile and Alfonso Baldi

Introduction

Endometriosis is characterized by the growth of endometrial glands and stroma at extrauterine sites, most frequently over visceral and peritoneal surfaces within the female pelvis [1]. It is a very common gynecological disorder present in up to 10% of women of reproductive age [2]. The incidence rises to 30% in patients with difficulties in conceiving [3]. Deep infiltrating endometriosis is a subset of endometriosis where the lesions are predominantly located under the peritoneal surface and is associated with intense pelvic pain symptoms [4]. Endometriosis is generally accompanied by chronic pelvic pain, adhesion formation, and infertility. It has been calculated that endometriosis is responsible for more than 100,000 hysterectomies each year in the United States with significant annual health-care costs attributable to this disease [3]. Moreover, the symptoms of this disease are mostly nonspecific and are very similar to those associated with other chronic pain disorders. As a result, in a great majority of cases, the definitive diagnosis is reached after several years and only by invasive surgical procedures, often with an incredible time interval between the onset of the symptoms and final diagnosis of 8–12 years [2, 3]. Original noninvasive approaches for the diagnosis of endometriosis have been recently proposed by our research group; however, this therapy is not yet standard of care [5–8]. Endometriosis remains a significantly underdiagnosed and undertreated disease and is considered a "social disease" since it has an important socioeconomic impact in view of the costs for the diagnosis and treatment, the loss of economic performance of the patients, and the negative impact on quality of life and capability of conceiving [2, 3].

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Pathogenesis of Endometriosis

Thanks to the work of Benagiano and Brosen and that of Knapp, the steps in the discovery and characterization of endometriosis in the history of medicine are now very well defined [9, 10]. Endometriosis has been a known entity for more than two centuries. In light of the significant social and economic impact this disease is known to have, it seems impossible that the pathogenesis of endometriosis has not been definitively elucidated. Currently, several pathogenetic theories have been proposed to explain the development and establishment of endometriosis. Table 8.1 summarizes the most commonly accepted theories for the histogenesis of endometriosis.

The most easily understood and widely accepted theory for the histogenesis of endometriosis is that of retrograde menstruation/transplantation, proposed one century ago by Sampson [2]. This theory hypothesizes that at menstruation, some effluent flows retrograde through the lumen of the Fallopian tubes into the peritoneal cavity, causing the adhesion and growth of endometrial fragments. This mechanism that considers endometriosis simply an autotransplant of normal endometrial tissue in an ectopic location in the organism explains the most common sites of endometriosis [2, 3]. Moreover, retrograde menstruation is a common phenomenon with more than 90% of women having blood in their pelvis at the time of menstruation [1]. Despite the fact that researchers have tried for decades to confirm this mechanism of histogenesis for endometriosis, no conclusive evidence has been produced in favor of this theory. More importantly, it fails to explicate the presence of endometriosis in such remote areas outside the peritoneal cavity, as the lungs, skin, lymph nodes, and breasts [2, 3]. Moreover, it is not an acceptable pathogenetic mechanism for endometriosis described in early puberty and in newborns [11], as well as in women affected by Mayer-Rokitansky-Küster-Hauser, a syndrome characterized by congenital aplasia of the uterus and the upper part of the vagina [12]. Finally, it cannot be considered a valid mechanism in the event of endometriosis in male, which is a rare but very well-described phenomenon with a total of 17 cases reported in the literature to date [13]. Nevertheless, elegant observations by Redwine propose that endometriotic tissue lacks characteristics of an autotransplant [14].

Table 8.1 Different theories proposed for the etiology of endometriosis

Theory	Mechanism proposed
Retrograde menstruation/ transplantation	Retrograde menstruation allows implantation of endometrial glands into the peritoneal cavity.
Coelomic metaplasia	Endometriosis arises in the pelvis or elsewhere by endometrial metaplasia of peritoneal mesothelium or other cell types.
Lymphatic and vascular dissemination	Spread of endometrial cells happens by lymphatic or hematogenous vessels.
Circulating stem cells	Transient pluripotent hematopoietic stem cells could differentiate into endometriotic tissue at different anatomical sites.
Embryonic cell remnants	Endometriosis originates from embryonic rests of the Mullerian ducts and Wolffian ducts.

The coelomic metaplastic theory suggests that endometriosis in the pelvis and elsewhere is caused by endometrial metaplasia of the peritoneal serosa or serosa-like structures, perhaps induced by environmental factors [15]. This theory would explain the cases where retrograde menstrual flow is impossible.

The lymphatic and vascular dissemination theory suggests the spread of endometrial cells by lymphatic or hematogenous vessels [15].

The theory of circulating stem cells claims that transient pluripotent hematopoietic stem cells could differentiate into endometriotic tissue at different anatomical sites [15].

The theory of embryonic cell remnants postulates that endometriosis originates from embryonic rests of the Mullerian ducts and Wolffian ducts. The Müllerian ducts, indeed, give rise to the female reproductive tract. This organogenesis is controlled by complex spatiotemporal molecular pathways, including the anti-Müllerian hormone signaling [15]. Aberrant differentiation or migration of the Müllerian ducts during embryogenesis could spread cells in their migratory pathway across the posterior pelvic floor, thus clarifying the observation that endometriosis is commonly found in the cul-de-sac, uterosacral ligaments, and medial broad ligaments.

This mechanism of histogenesis was proposed by pioneer scientists of this disease in the late nineteenth and twentieth century but inexplicably forgotten after the advent of Sampson's retrograde menstruation theory [9, 10]. Table 8.2 summarizes the most important observations supporting the embryological theory in chronological order as clearly described by the works of Benagiano and Brosens and Knapp [9, 10]. Further supporting evidence of the fetal origin is the observation that the cells of pubertal or postpubertal clinical endometriosis maintain some typical characteristics of fetal endometrium cells, such as ontogenic resistance to progesterone [16]. This characteristic is, obviously, not present in the mature adult endometrium.

Recently, work from our research group and others have demonstrated the presence of ectopic endometrium in a significant number of human female fetuses [17–19]. These scientific evidences clearly support the embryogenetic theory. In this

Table 8.2 Observations supporting the embryological origin of endometriosis, performed by pioneer scientists of this disease in the late nineteenth and twentieth century, as described in the work of Benagiano and Brosens [10] and Knapp [9]

Author	Mechanism proposed	References
Von Reckinglausen 1893	Wolffian origin	Dtsch med Wochenschir 1893; 46: 825.
Orloff 1895	Embryonic cells	Zeitschr Heilkunde 1895; 5: 121.
Pick 1897	Mesonephric origin	Arkiv f Gynäk 1897; 54: 119.
Kossman 1897	Mullerian origin	Archiv f Gynäk 1897; 54: 359.
Mayer 1903	Epithelial heterotopy	Z Geburtshilfe Gynäkol 1903; 49: 32.
Schikele 1904	Mesonephric origin	Zentralbl Allg Pathol Anat 1904; 15: 261
Cullen 1908	Mucosal theory	WB Saunders 1908
Frankl 1911	Mullerian origin	Arkiv f Gynäkol 1911; 93: 659
Lockyer 1918	Mullerian origin	MacMillan and Co, 1918

chapter, we describe the most salient data produced by our research group and other scientists regarding fetal endometriosis in order to better determine the real biological impact of this phenomenon.

Fetal Endometriosis

Our research group has demonstrated the presence of ectopic endometrium in a significant number of human female fetuses (10 in 101 cases) analyzed by autopsy in three different works [17–19]. These structures were found outside the uterine cavity and could not be attributed to any normal anatomical formation. In particular, the anatomical sites of these endometrial structures were in the mesenchymal tissue close to the posterior wall of the uterus, in the proximity of the Douglas pouch, in the rectovaginal septum, in the rectal tube at the level of muscularis propria, and in the wall of the uterus. Interestingly, all of these anatomical sites are very well-known locations for endometriosis in women [1]. Immunohistochemical studies were utilized to assist in the evaluation and characterization of these endometriotic structures. These organoid lesions demonstrated positive staining for CA-125, cytokeratin 7, and estrogen receptor in the epithelial component, while the stromal cells displayed positive staining for both CD-10 and estrogen receptor. Fetal endometrium was also evaluated in these patients and revealed identical staining patterns. The exact anatomical distributions of all the endometriosis-like structures found in these three works are depicted in detail in Fig. 8.1. An example of the histological and immunohistochemical appearance of this ectopic endometrium is reported in Figs. 8.2, 8.3, 8.4, and 8.5. Based on the anatomical location, and on the histological and immunohistochemical characteristics, these structures must be ascribed to endometrial tissue, dislocated outside the uterine cavity during the earlier steps of organogenesis and displaying a molecular immunophenotype identical to that of the endometrium present in the uterus. To the best of our knowledge, these observations have been the first direct and systematic demonstration of the theory of embryonic cell remnants as the cause of endometriosis.

After our data was published, subsequent studies also confirmed the presence of endometriotic structure in female fetuses. In the work by de Jolinière et al., the reproductive organs of seven female fetuses were analyzed at autopsy [20]. In two out of seven fetuses, ectopic endometrial glands were found in the myometrium, while several ectopic endometrial glands surrounded by stroma were found in the uterine broad and ovarian ligaments and under the fallopian tube serosa in six fetuses. These glandular structures expressed positive staining for estrogen and progesterone receptors, while the stromal components displayed positive staining for CD-10 and vimentin [20].

Nevertheless, Schuster and Mackeen have reported a case of fetal endometriosis diagnosed as a large fetal pelvic mass at 35 weeks of gestation [21]. The mass was surgically removed on the second day of life, and histological examination of the specimen confirmed the diagnosis of cystic endometriosis of the left ovary [21].

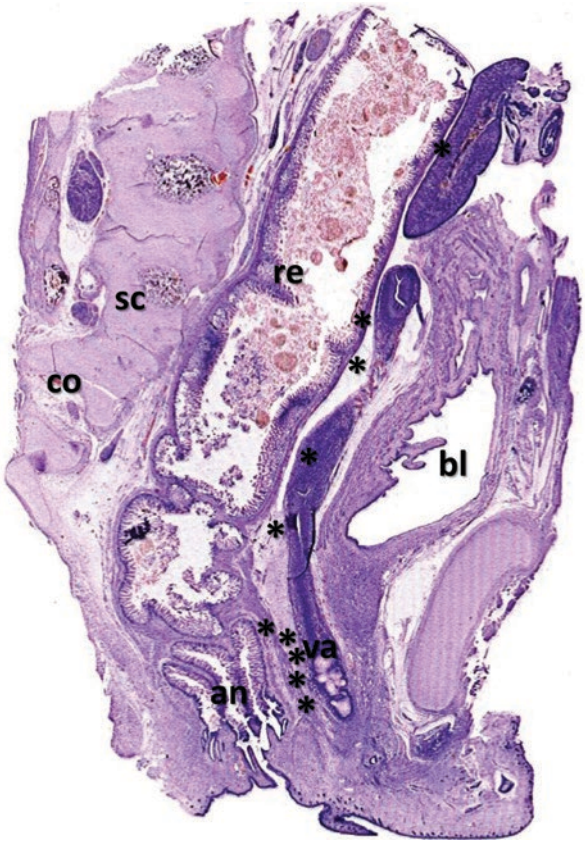

Fig. 8.1 Anatomical distribution of the ectopic endometrium found in the female human fetuses in the works by Signorile et al. (see references 24–26) Representation of the pelvic organs of a female fetus at around 25 weeks of gestation, displaying the anatomical location of the endometriotic structures. The different locations are indicated by asterisks in the proximity of the Douglas pouch, in the mesenchymal tissue close to the posterior wall of the uterus, in the rectal tube at the level of muscularis propria, in the wall of the uterus, and in the rectovaginal septum Abbreviations used: an anus, co coccyx, va vagina, re rectum, sc spinal column, ut uterus, bl bladder (Modified from Signorile et al. [18])

If we analyze the scientific literature preceding the above-described work on fetal endometriosis, we find some anecdotal scientific observations [22, 23]. Moreover, the presence of endometriosis in the fetus was hypothesized, but not demonstrated, by Batt et al. with the mullerianosis theory, even if this phenomenon was considered as different from endometriosis [24]. Based on our data and the observation of others regarding the presence of ectopic endometrium in the fetus, we believe these endometriotic structures remain quiescent and asymptomatic until puberty, at which time the hormonal inputs result in activation and, consequently, the onset of the symptoms of endometriosis [15]. The molecular mechanisms responsible for the histogenesis of these ectopic endometrial structures, as well as their survival until puberty, are largely unknown. As far as pathogenesis is concerned, it is possible to hypothesize that complex molecular mechanisms, also regulated according to a precise spatiotemporal scheme, can be altered by abnormal inputs that act on an adequate genetic background in a specific organogenesis window of time. We consider this phenomenon as an alteration of the fine-tuning of female genital structures organogenesis caused by genetic and epigenetic factors that would cause disruption of some organizational events associated with

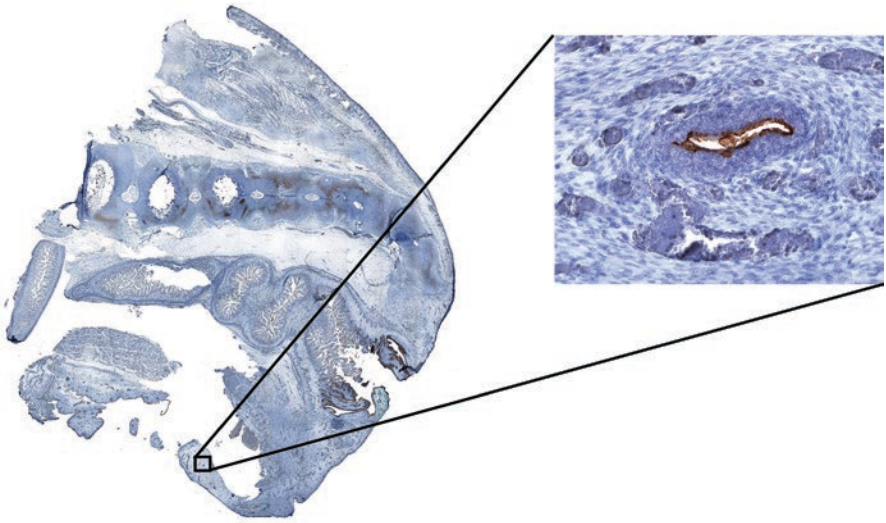

Fig. 8.2 Histological and immunohistochemical appearance of ectopic endometrium in a female human fetus of 25 weeks
The picture shows an endometrial structure in the rectovaginal septum; in the inset, the immunohistochemical expression of estrogen of this structure at higher magnification is depicted. (Modified from Signorile et al. [17])

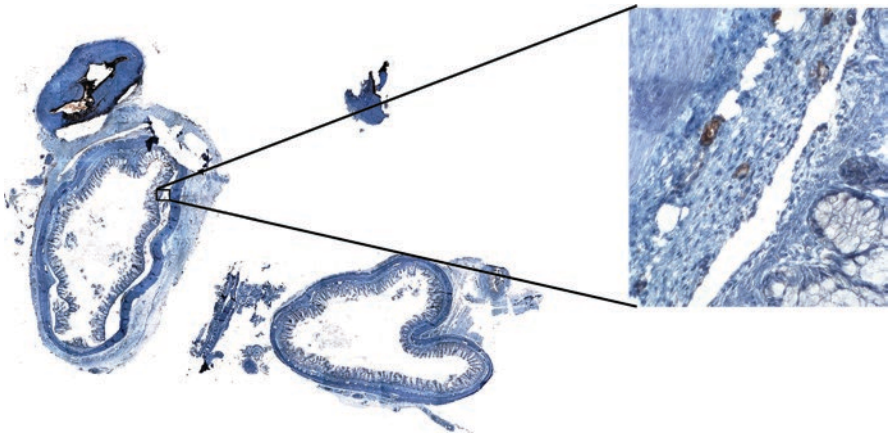

Fig. 8.3 Histological and immunohistochemical appearance of ectopic endometrium in a female human fetus of 24 weeks
The image shows an endometrial structure in the proximity of the Douglas pouch; in the inset, the immunohistochemical expression of estrogen receptor of this structure at higher magnification is depicted. (Modified from Signorile et al. [17])

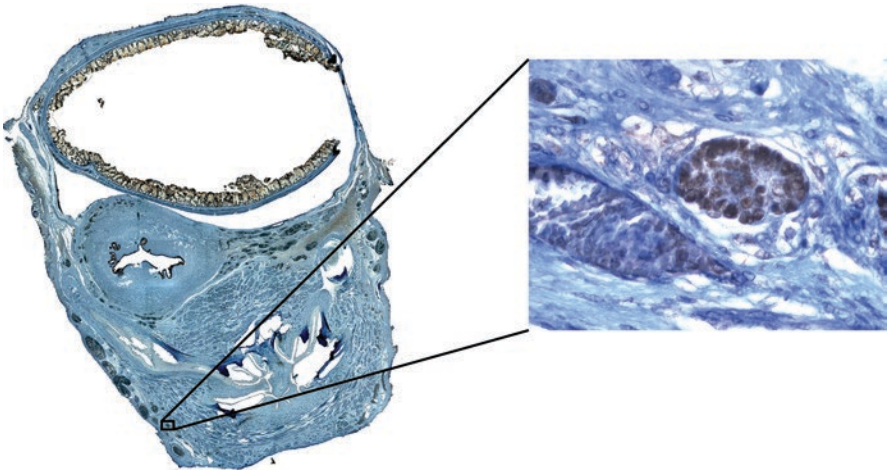

Fig. 8.4 Histological and immunohistochemical appearance of ectopic endometrium in a female human fetus of 18 weeks
The picture shows an endometrial structure in the rectal tube at the level of muscularis propria; in the inset, the immunohistochemical expression of CA-125 of this structure at higher magnification is depicted. Note that the epithelium of the rectum is negative for CA-125. (Modified from Signorile et al. [17])

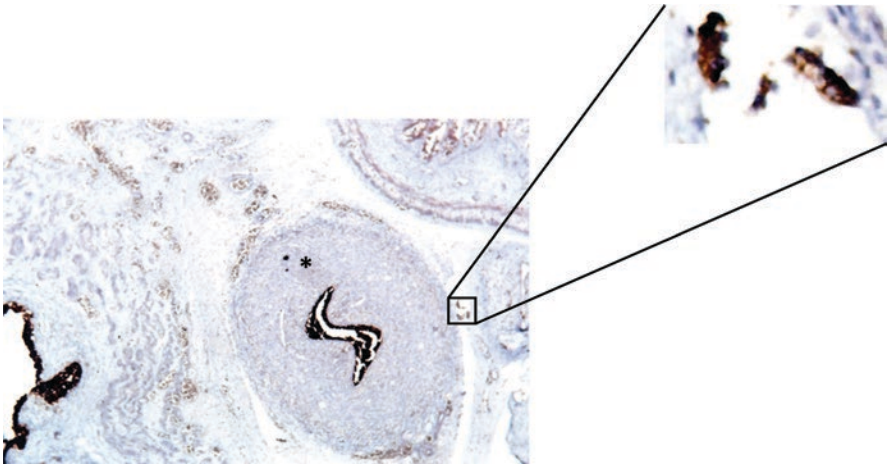

Fig. 8.5 Histological and immunohistochemical appearance of ectopic endometrium in a female human fetus of 16 weeks
The image shows an endometrial structure in the mesenchymal tissue close to the posterior wall of the uterus; in the inset, the immunohistochemical expression of CA-125 of this structure at higher magnification is depicted. Note that in the wall of the primitive myometrium is present a little group of endometrial cells positive for CA-125 (indicated by an asterisk) that could represent a primitive nest of adenomyosis. (Modified from Signorile et al. [17])

development of the normal neonatal uterine wall [25]. The observation that endometriosis is significantly higher in patients affected by uterine malformations, such as Müllerian anomalies, anogenital distance, myometrial structural alterations, and other genital anomalies, is indirect support of this proposed mechanism [25]. Recently, works by Makiyan [26] have suggested that the origin of endometriosis is from primordial germ cells; this observation further supports the presence of endometriosis in the fetus.

If we consider the fact that the most important hormone in the female genital tract morphogenesis is estrogen, it is likely that altered estrogenic input may be one of the factors responsible for the histogenesis of fetal endometriosis [25]. There are important epidemiological and experimental studies that link the onset of endometriosis, as well as other changes in the female genital system, to exposure in utero to endocrine disruptors, substances capable of mimicking the action of the hormone estrogen. In this regard, it is important to remember the epidemiological work of Missmer, which demonstrated a significantly higher number of cases of endometriosis in female patients exposed in utero to diethylstilbestrol [27] as well as experimental data from our group showing an endometriosis-like phenotype in mice exposed in utero to the endocrine disruptor bisphenol [28]. Finally, through experimental approaches of genomics, we have been able to reveal a specific pattern of gene expression in the tissue of endometriotic structures compared to normal endometrial tissue. This specific gene expression pattern essentially concerned genes involved in embryogenesis and was not modified by the phases of the hormone cycle [15].

Conclusions

Endometriosis is a multifactorial disease with many-sided features, and accordingly, the pathogenesis could be slightly different in different cases. The proposed theories of pathogenesis are perhaps not mutually exclusive and may be interrelated. Nevertheless, the recent findings reviewed in this chapter lend a compelling argument to the embryogenesis theory especially when compared to the retrograde menstruation theory. The clinical and therapeutic implications are relevant. In particular, recurrence of the disease should not be ascribed to retrograde menstruation but rather to an incomplete surgery due to the presence of microscopic foci and/or at a different timing in the growth of the various foci in the same patient. This last phenomenon is very common in diseases induced by endocrine disruptors and is probably due to individual susceptibility. Even more important, treatment of the disease with synthetic estrogens or selective estrogen receptor modulators chemical compound is, indeed, effective in reducing the symptoms but could cause the growth of microscopic lesions and exacerbate the disease. A more complete understanding of the molecular mechanisms responsible of the pathogenesis of endometriosis could, hopefully, individuate suitable therapeutic targets for this still “uncurable” disease.

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Part IV
Diagnosis

Chapter 9
Clinical Evaluation and Preoperative Considerations in Adolescent Girls with Endometriosis

Nkiruka Chuba and Resad Pasic

Introduction

Increasing evidence suggests that endometriosis is more common than previously believed in prepubertal and adolescent females, although the presence of endometriosis-like illness in young girls has been seen and recognized since the days of Hippocrates [1]. When developing a differential diagnosis for chronic pelvic pain, the clinician must maintain a broad differential including gynecologic, genitourinary, musculoskeletal, neuropathic, gastrointestinal, and psychological etiologies. This differential is further narrowed by consideration of the patient's age, symptoms, physical examination findings, and imaging. Many unanswered controversies regarding the prevalence, natural course, and management of endometriosis still exists; however, an increasing number of reports in the literature have resulted in a better understanding of this chronic disease. In this chapter, the focus is on the key components of clinical evaluation as well as preoperative considerations in the diagnosis, evaluation, and management of endometriosis among prepubertal and adolescent females. A detailed description of the medical and surgical management options will be presented in other chapters.

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Epidemiology

Endometriosis is thought to affect approximately 10% of reproductive-age women [2]. Specifically, 38% of infertile women and up to 70% of women with chronic pelvic pain for 6 months or more in duration have endometriosis with no clear racial or ethnic predisposition [3]. The true incidence and prevalence of endometriosis in the prepubertal and adolescent population remain unknown. Wide variations in disease prevalence likely exist due to variable diagnosis (pathology-proven versus self-report), differences in visual detection rates at the time of diagnostic laparoscopy, and lack of correlation between disease severity and symptomatology [4].

According to the American Academy of Pediatrics, adolescence is defined as the period following the onset of puberty and adulthood that occurs between 12 and 21 years of age [5]. There is an increasing body of literature that suggests endometriosis is more prevalent and can occur earlier than previously believed in this population. A systematic review of 15 articles published between 1980 and 2011, involving 880 adolescent girls with chronic pelvic pain or dysmenorrhea who underwent diagnostic laparoscopy, calculated the prevalence of visually confirmed endometriosis as 62%. This prevalence increased to 70% in girls with dysmenorrhea alone, and 75% in girls with chronic pelvic pain resistant to conservative medical therapy [6]. There have been several case reports in which biopsy-proven endometriosis was identified at the time of laparoscopy in premenarchal girls [7]. One such case includes the diagnosis of an ovarian endometrioma in an 11-year-old girl prior to the onset of menses [8].

Pathophysiology

Endometriosis is defined as a gynecologic disease characterized by the presence of glands and/or endometrial stroma outside the uterine cavity [9]. Histologic confirmation at the time of surgical evaluation is traditionally regarded as the gold standard for the diagnosis of endometriosis. Several theories for the pathogenesis of endometriosis exist; however, ultimately the disease etiology is likely multifactorial as no one theory can explain all cases of endometriosis. Regardless of the inciting theory, endometriosis involves the release of prostaglandins and leukotrienes which cause inflammation, vasoconstriction, and myometrial contractions, leading to ischemia and pain [10].

The most widely accepted theory is retrograde menstruation originally proposed by Sampson in which viable endometrial cells are extruded from the fallopian tubes into the peritoneal cavity at the time of menstruation and implant on extra-uterine viscera [11]. This theory would suggest a greater prevalence of endometriosis as most asymptomatic women actually experience some degree of retrograde menstruation with each menstrual cycle. This theory alone does not explain why some women are at increased risk of development of endometriosis while others are

spared as all women with uterus menstruation but not all have endometriosis [12]. The retrograde menstruation theory also does not explain the presence of endometriosis in women with disease onset prior to menarche, or in women with Müllerian agenesis, aplasia, or obstructive anomalies [13, 14].

Other leading theories include Halban's (1924) theory of lymphatic or vascular transport of endometrial fragments, Meyer's (1919) theory of coelomic epithelial metaplasia from an unspecified stimulus as both peritoneal and endometrial cells are derived from the same embryonic progenitor cells, the theory of hormonal milieu which assumes activation of ectopic epithelial cells in the presence of circulating steroid hormones [15], and finally the theory of genetic predisposition versus immune system dysfunction [14].

An emerging theory of neonatal uterine bleeding postulates that early-onset endometriosis in prepubertal girls may in fact have a different origin from that of the adult woman. Here naive endometrial progenitor cells seed the peritoneal cavity, implant, and remain dormant until thelarche, during which time they are activated by unknown factors [16].

Clinical Presentation and Evaluation

The adolescent patient may present to either a pediatrician or gynecologist for initial evaluation. Gynecologists are familiar with the clinical presentation and evaluation of pelvic pain in an adult woman but may not be as comfortable with diagnosing endometriosis in the adolescent. Although there are many similarities, endometriosis may manifest itself differently outside of the adult population. The evaluation of adolescents with pelvic pain may seem daunting; however, a diagnosis may be made in a timely fashion by obtaining a detailed history and physical examination, utilizing clinic-based tests and imaging studies, as well as maintaining a high index of suspicion.

Pelvic pain may be cyclic or acyclic in nature, and sexually active teenagers may report dyspareunia and in rare cases may report infertility. The most common types of pain in adolescents with endometriosis are chronic pelvic pain and dysmenorrhea. Fifty to 90% of adolescent girls and young women will experience primary dysmenorrhea [17]. With such a high prevalence of pelvic pain, the distinction between normal and pathologic processes, such as endometriosis, adenomyosis, Müllerian anomalies, an obstructed reproductive tract, adnexal masses, vaginismus or other pelvic floor disorders, and infections, is more difficult.

The initial evaluation requires a thorough history. History should include a medical, gynecologic, family, and psychosocial history. A thorough family history is a key component of the history as the incidence of endometriosis in patients with an affected first-degree relative is 6.9% suggesting a genetic predisposition [18]. The onset of pain, its location, characterization, chronicity, association with menses or moliminal symptoms, and the presence of associated symptoms such as nausea, emesis, headaches, sleep disturbance, constipation, diarrhea, dyschezia, hematochezia,

dysuria, frequency, dysuria, or hematuria should also be assessed as these often suggest secondary dysmenorrhea or a pathologic abnormality [19]. A pain diary may prove beneficial in this setting [20]. Although rare, extra-pelvic endometriosis may present as abdominal pain, referred pain to the shoulder(s) from diaphragmatic endometriosis implants, chest pain, or pain with breathing that may correlate to menses. Finally, pain may have negative effects on one's physical and psychological functioning leading to recurrent absences from school, lack of participation in extracurricular activities, increased anxiety, or depression [21, 22].

During the physical examination, a pelvic exam is often not required in the non-sexually active female, especially if there is no concern for an obstructive process contributing to pain or if the concern for pelvic infection is low. Adolescents and gynecologic providers may be wary of the possibility of a pelvic examination. It is important to build rapport with the patient prior to pursuing a physical exam, which may require more than one clinic visit to accomplish. Nonetheless, the patient should be reassured that an internal exam is not required to evaluate or treat endometriosis. A Q-tip test with gentle insertion into the vaginal canal to ensure an adequate vaginal length ruling out vaginal agenesis or a transverse vaginal septum may be performed [23]. In circumstances in which the Q-tip test is not feasible or the patient declines or is unable to tolerate the exam, a transabdominal ultrasound or the more informative pelvic MRI should be performed if an anomaly is suspected to further elucidate the anatomic defect and guide management. The need for an imaging study should be individualized as endometriotic lesions, with the exception of deeply infiltrating endometriosis and endometriomas, are not routinely diagnosed through ultrasonography, computerized tomography (CT scan), or magnetic resonance imaging (MRI).

The use of biochemical markers such as CA 125, ICAM, IL-6, and CA 19.9 remains controversial but with further research may result in a noninvasive tool to make a timely diagnosis of endometriosis in patients presenting with chronic pelvic pain and dysmenorrhea [15]. Laboratory tests including a pregnancy test, urinalysis, urine culture, or testing for sexually transmitted diseases should be obtained when appropriate.

Management

Endometriosis is a chronic condition, and to date there is no cure and no single optimal management option. Management is traditionally divided into medical and surgical modalities; however, both are often required to treat and manage symptoms effectively. The goal of treatment should be to decrease pain, reduce recurrence, preserve future fertility, and minimize risk of loss of select organ function.

The differential diagnosis for chronic pelvic pain is broad. When the initial evaluation does not suggest a bowel, bladder, or neuromuscular concern, empiric therapy is recommended. First-line therapy in adolescents with endometriosis or in cases in which endometriosis is suspected includes nonsteroidal anti-inflammatory

drugs (NSAIDs) for analgesia. The addition of a hormonal agent supplemented with NSAIDs is also recommended to improve symptoms. Combined oral contraceptive pills (COCPs) in a continuous fashion are recommended as a first-line hormonal option [24], although long-term success with cyclic use has also been appreciated. Alternative agents include the contraceptive patch, vaginal ring, etonogestrel subdermal implant, subcutaneous depot medroxyprogesterone acetate, and levonorgestrel intrauterine devices (LNG-IUD). Use of progestins in the adult population has been shown to improve symptoms related to endometriosis; however, there is a lack of long-term data on the use of progestin-only methods, particularly oral formulations, in adolescents.

The use of gonadotropin-releasing hormone (GnRH) agonists remains controversial and is not routinely recommended for empiric use in adolescents. Caution should be exercised for long-term GnRH agonist use in adolescents under 17 years of age due to detrimental effects on bone mineral density [25]. A trial of GnRH agonists is not recommended to diagnose endometriosis given its adverse side effect profile, and it is often poorly tolerated even with add-back therapy.

Complementary and alternative therapies including heat or cooling therapy, regular exercise, dietary or herbal supplementations, transcutaneous electrical nerve stimulation, yoga, and acupuncture may also be considered; however, further research is needed to establish their effectiveness [19]. Each method has unique benefits, risks, and potentially adverse side effects, and as such, the decision to use a particular method should be individualized. It is also important to keep in mind that improvement on an empiric medical regimen does not confirm a diagnosis of endometriosis, and patients may benefit from trying different types of hormonal therapies until the best fit is found. Pain that is resistant to medical therapy raises suspicion for endometriosis.

Preoperative Considerations

A definitive diagnosis with laparoscopy and visualization as well as a formal histologic confirmation remains the gold standard. If there is no improvement in symptoms within 6 months of treatment with NSAIDs and combination OCPs, further investigation into possible secondary etiologies, treatment compliance, trial of alternative hormonal therapy, and, finally, diagnostic laparoscopy is strongly considered for the evaluation and treatment of possible endometriosis [26]. Laufer et al. recommend, when working with adolescents, surgical evaluation with laparoscopy should be performed prior to a full 3–6 trial of empiric hormonal therapy [27].

Unfortunately, even in adult women, the diagnosis of endometriosis may be delayed for years. According to a study by Nezhat et al., the average time from the onset of symptoms until diagnosis was 22.8 months over a median of three physician visits [28]. Understandably many gynecologists are hesitant to subject adolescents to surgical intervention. If the physician is not comfortable with the management of endometriosis at the time of surgical evaluation, the patient should

be referred to a gynecologist, pediatric gynecologist, or pediatric surgeon with expertise in management of this condition. Ultimately, laparoscopy is no different than in the adult population as both adolescents and adult women present in various shapes, sizes, and weights [23]. To optimize cosmesis and to position ports, a comfortable confirmation to perform diagnostic laparoscopy, the optical trocar is placed through an incision at the base of the umbilicus with an operative port placed about 2 cm above the pubic symphysis for manipulation [27]. The method of initial entry at the umbilicus (Veress needle, Hasson, or direct entry) as well as placement of additional operative ports to optimize access to remove or ablate endometriotic lesions is at the discretion and comfort level of the surgeon.

The American Society of Reproductive Medicine (ASRM) has described and classified the variable morphology of endometriosis [29]. There is no clear correlation between disease severity and the amount of pain experienced. A clear understanding of the difference in appearance of endometriotic lesions between adults and adolescents is key to making a diagnosis at the time of surgery. In adolescents, endometriosis typically appears as clear or red vesicular lesions or peritoneal Alan-Masters defects. Looking for brown, black, powder-burn, or pale fibrotic lesions, which represent older implants, will lead to underdiagnosis and inadequate treatment.

Several techniques exist to aid in identification of these often elusive endometriotic lesions. The magnification technique involves placing the laparoscope within millimeters of the peritoneum, while filling the pelvis with sterile saline and submerging the laparoscope to help distinguish the clear, shiny vesicles from normal peritoneum [30]. Endometriosis is usually staged according to the revised ASRM classification system when visualized. If no evidence of endometriosis is seen after thorough investigation of the pelvis, a cul-de-sac biopsy should be performed to rule out microscopic disease. Peritoneal stripping in adolescents is not recommended due to theoretical concerns of adhesion formation leading to bowel obstruction, worsened pelvic pain, and compromised fertility [19]. This risk may be mitigated with use of adhesion barriers, although more short- and long-term data are needed to determine effectiveness. Removal of lesions may be performed with excision, electrocautery, or laser ablation. This will depend highly on the skill and comfort of the surgeon, the location of the lesion, and type of lesions identified. Laparotomy is rarely indicated.

The goal of surgical treatment is to minimize disease burden, reduce pain, and improve quality of life. Selecting the best method of surgical management of endometriosis is challenging. Considerations should be given to the type (deeply infiltrative endometriosis, superficial lesions and endometriomas), location, and severity of disease, patient age, symptoms, potential complications, and desires for future fertility. Biopsy or surgical excision of at least one lesion is recommended to confirm histologic diagnosis of endometriosis. An understanding of the modalities of laparoscopic ablation and excision as well as pelvic anatomy is paramount to avoiding potential risk of injury to surrounding structures including the ureters, bowel, bladder, and major vasculature. In addition, familiarity with surgical instruments, the energy utilized and the variable depth, and tissue spread will aid in reducing short- and long-term surgical complications.

A 2014 systematic review and meta-analysis of 10 randomized control trials involving 973 women with mild to moderate disease on visual inspection reported an improvement in pain at 6 and 12 months in the surgical group compared to controls who underwent diagnostic laparoscopy alone [31]. Similar findings were confirmed in a 2017 systematic review which compared excision versus ablation on pain outcomes showing improvement in dysmenorrhea, dyschezia, and dyspareunia among the excision group at 12 months after surgery [32]. A 2014 prospective, randomized, double-blinded study evaluating the reduction of pelvic pain after laparoscopic ablation versus excision of endometriosis reported a reduction in overall pain scores in both groups at 5 years postoperatively; however, the ablation group required long-term supplemental medical treatment [33]. Laparoscopic excision of the cyst wall of endometriomas greater than 3 cm in size has been shown to reduce pain and disease recurrence over ablation alone [34]. Treatment decisions should be individualized through shared decision-making after a detailed discussion of available treatment options and goals.

The risk of recurrence of pelvic pain symptoms, indicative of recurrent disease, is of great concern, and this may lead to further suffering, need for reoperation, and frustration on the part of the patient and the physicians. Young age has been established as an independent risk factor for endometriosis recurrence after surgical treatment alone [35]. Surgical intervention alone is not considered adequate or appropriate treatment as there may be residual microscopic disease that persists, requiring hormonal suppression to further reduce the risk of recurrence and disease progression [23, 25, 36].

Conclusion

Adolescent and prepubertal endometriosis is more common than previously thought and is a significant cause of cyclic and acyclic chronic pelvic pain. The diagnosis of endometriosis in this population requires a high index of suspicion, a thorough history and physical examination, and careful utilization of laboratory and imaging modalities where appropriate. It is important to start empiric therapy with NSAIDs and hormonal treatment initially. Consider diagnostic laparoscopy for definitive diagnosis and management with the understanding that endometriosis is a chronic disease and will often require long-term hormonal treatment to reduce the risk of disease recurrence and progression.

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Chapter 10
Neuroanatomical Insights in Adolescents with Endometriosis and Pain

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Pain is an unpleasant subjective experience and it is difficult to quantify. The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Types of Pain

Nociceptive, inflammatory, and neuropathic pain are the most clinically important biologic mechanisms of pain. Nociceptive pain is the normal response to a noxious stimulus that alerts the organism to impending or actual tissue injury. Inflammatory pain is due to the response to tissue injury and the resulting inflammatory process, a common characteristic of endometriosis. Inflammatory pain may become chronic or persistent and represents a pathologic pain mechanism. Neuropathic pain is generated by damage to or dysfunction of neurons in the peripheral or central nervous system. It occurs independent of any provoking event and frequently leads to a chronic pain state. Central sensitization and peripheral sensitization can be considered as parts of neuropathic processes implicated in chronic pain, including chronic pelvic pain associated with endometriosis. Central sensitization is an increased

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responsiveness of pain transmission by neurons in the spinal cord and is usually caused by neurochemical changes in the spinal cord and brain stem. Peripheral sensitization is a compromised state of nociceptor function, characterized by a lowered threshold of activation and by an increased response to stimuli.

Nociceptive Pain

Stimuli that have the potential to cause damage (e.g., thermal, mechanical, or chemical stimuli) produce cutaneous pain by acting on primary afferent nociceptors; these are the initial structures involved in nociceptive processes. Nociceptors are physiologically specialized peripheral sensory neurons that respond to noxious stimuli. These are free, unencapsulated peripheral nerve endings found in most tissues of the skin, muscle, connective tissues, blood vessels, and viscera [1, 2].

This "noxious" information is transduced by the receptors into an electrical signal and transmitted from the periphery to the central nervous system along axons. There are two types of nociceptors: (1) high-threshold mechanoreceptors (HTM), which respond to mechanical deformation, and (2) polymodal nociceptors (PMN), which respond to a variety of tissue-damaging inputs: hydrogen ions, 5-hydroxytryptamine (5-HT), cytokines, bradykinin, histamine, prostaglandins, and leukotrienes [3]. Other factors such as nerve growth factor and cytokines are also important at the peripheral level, and resultant changes in the phenotype of the sensory neurons can alter their responsiveness [4].

Nociceptors are therefore the free nerve endings of nerve fibers. There are two main fiber types: A-delta and C-fibers. C-fibers (<2 mm diameter) are unmyelinated with a conduction velocity of less than 2 m/s and are associated with prolonged "burning" pain. However, not all unmyelinated fibers are nociceptors: some respond to heat in the non-noxious range, and some are activated by non-noxious mechanical stimuli. The other major group of nociceptors are thinly myelinated A-delta fibers, which have a diameter of 2–5 mm and a conduction velocity of 6–30 m/s and are associated with a more brief "sharp" pain. Most small-diameter primary afferents are mechanically sensitive although some are sensitive to thermal stimuli. Approximately 10% of cutaneous myelinated fibers and 90% of unmyelinated fibers are nociceptive [1]. These primary afferent nerve fibers have cell bodies in either the dorsal root ganglia or trigeminal ganglion and terminate in the dorsal horn of the spinal cord. Although all pain fibers terminate in the dorsal horn, their route to this endpoint varies. Most enter the dorsal horn in the ventrolateral bundle of the dorsal root. They travel just lateral to the larger-diameter myelinated A-beta fibers, which respond to non-painful stimuli such as vibration and light touch. However, 30% of the C-fibers enter the spinal cord via the ventral root. Once they have entered the spinal cord, the nerve roots may bifurcate into ascending and descending branches, which can enter the dorsal horn one or two segments higher or lower than the

segment of origin. Brief cutaneous stimuli can result in separate and distinct sensations, which are sometimes referred to as “fast” and “slow” pains. Fast pain is thought to be caused by activation of faster-conducting cutaneous A-delta fibers and is perceived as a short-lasting, pricking type of pain. Slow pain is believed to be caused by the activation of slower-conducting cutaneous C-fibers and is perceived as a dull, poorly localized, burning type of pain [5, 6].

Pathways of Nociceptive Pain

Central Level (Forebrain/Midbrain)

Pain from peripheral nerve injury, inflammation, and cancer, characterized by ongoing pain, hyperalgesia, and allodynia, arises from peripheral and then central spinal processes, but the brain determines the level of pain perceived. Certain spinal neurons project to thalamus and cortex and generate the sensory aspects of pain and the location and intensity, while others project in parallel to limbic areas [6].

The thalamus represents the main relay structure for sensory information destined to the cortex and involved in the reception, integration, and transfer of the nociceptive potential. The different projections to its nuclei and from them to the cortex define the functional circuitry of pain processing [5].

Axons travelling in the lateral and medial spinothalamic tracts terminate in their respective medial and lateral nuclei, and from here neurons project to the primary and secondary somatosensory cortices, the insula, the anterior cingulate cortex, and the prefrontal cortex. These areas play various roles in the perception of pain and also interact with other areas of the brain, for example, the cerebellum and basal ganglia (which are areas more traditionally known to be associated with motor function rather than pain) [3]. The centromedian nucleus projects more diffusely, including projections to the limbic system, and is believed to be involved in the affective-motivational aspects of pain. This widely distributed cerebral activity reflects the complex nature of pain involving discriminative, affective, autonomic, and motor components [1].

The insula receives impulses from the lateral system, and its projection pathway is directed at the limbic system, amygdala, and some regions of the prefrontal cortex related to the emotional and affective component and to memory inherent to the painful experience. It is also considered to be a somatic motor visceral area because it acts as a sensory component of integration between visceral, vestibular, and tactile sensations [7]. The anterior cingulate cortex plays a pivotal role bringing the attentional and emotional mechanisms to pain experience. Its coordinate inputs from parietal areas with frontal cortical regions which integrate the perception of bodily threat with the strategies and response priorities of pain behavior [8, 9].

Spinal Cord (Medulla) Level

The release of transmitter into the spinal cord allows spinal neurons to be activated through postsynaptic receptors, which in turn activate local motor reflexes and parallel ascending projections to the brain to produce the sensory-discriminative and affective components of pain [4]. It plays a crucial role in the modulation of pain processing at the spinal cord level. Pathways originating in the cortex and thalamus are relayed via the rostral ventromedial (RVM) medulla and adjacent areas to the dorsal horn of the spinal cord [2].

These pathways have a role in the modulation of pain. Noradrenaline and 5-HT are the key neurotransmitters involved in descending inhibition. Two important areas of the brain stem are involved in reducing pain: the periaqueductal grey (PAG) and the nucleus raphe magnus (NRM). The balance between the descending facilitatory and inhibitory pathways is subject to change following injury, and an imbalance has been implicated in the development of chronic pain states [3].

The different ascending bundles form two phylogenetic different systems. The first, older one, runs through the medial region of the brain stem and is formed by the paleospinothalamic, spinoreticular, spinomesencephalic, spinoparabrachial-amygdaloid, spinoparabrachial-hypothalamic, and spinohypothalamic bundles. The other system, more recent, occupies the lateral region of the brain stem and consists of the neospinothalamic bundle, spinocervical bundle, and postsynaptic beam of the dorsal horn [10].

The spinothalamic tract is regarded as having a central role in pain perception and transmits information regarding pain, cold, warmth, and touch. In the medulla, the bodies of these neurons are located in larger numbers in laminae I and V but are also found in laminae II, IV, VI, VII, VIII, and X [11]. Fibers arising from more caudal segments tend to be located laterally, and those entering from more rostral segments tend to be located in the more medial and ventral part of the tract. They respond well to noxious mechanical and thermal stimuli, but many also respond to non-noxious mechanical stimuli [3].

The spinoreticular tract originates mainly in laminae V, VII, and VIII and also in laminae I and X. Many spinoreticular neurons are activated preferentially by noxious input, but there is no clear somatotopic organization of the spinoreticular tracts [12]. The sites of termination of this tract suggest that some of its components are involved in a range of more organized and integrated motor, autonomic, and antinociceptive responses to noxious input, such as orienting, quiescence, defense, and confrontation. The afferences of spinoreticular tract are involved in the motivational-affective characteristic, as well as the neurovegetative responses to pain [13].

The cells of origin of the spinomesencephalic tract are located predominantly in laminae I and IV–VI of the dorsal horn, with some found in lamina X and the ventral horn. These cells project to several nuclei in the midbrain, including the PAG, cuneiform nucleus, red nucleus, superior colliculus, pretectal nuclei, and Edinger-Westphal nucleus. A pattern of excitation followed by inhibition is commonly observed when stimulating the PAG, as well as other regions of the midbrain. This

suggests an autoregulatory medullary/midbrain activity with different connections and velocities of propagation [14].

In addition to the characteristics of somatosensory processing and activation of the mechanisms of descending analgesia, the stimulation of regions innervated by the spinomesencephalic tract produces different responses implicated in nociceptive processing. Thus, stimulation of these regions is capable of provoking aversive behaviors in the presence of noxious stimuli and motor responses of the visual desertion type, besides autonomic, cardiovascular, motivational, and affective responses [14, 15].

The dorsal columns and nuclei (gracile and cuneate nuclei) are generally considered to be the pathway for information regarding the non-noxious sensations of fine touch, proprioception, and vibration. Extensive direct and indirect projections are described for the gracile nucleus, which plays an important role of sensory integration of the projections from abdominal organs and from the skin and then projecting to the thalamus. The pathway that supplies this information is referred to as the postsynaptic dorsal column pathway and has cells of origin in lamina III of the dorsal horn as well as just lateral to lamina X. Damage to large myelinated fibers results in the de novo synthesis of substance P within these neurons and may be part of the mechanism responsible for the hypersensitivity to light touch that occurs following peripheral nerve injury.

Peripheral Level

When an A-delta or C-fiber is cut or partially damaged, it tries to repair itself, and then there is a cascade of events involving primary sensory afferents, sympathetic efferents, white blood cells, and platelets that induce peripheral sensitization. After the initial damage, it does not heal in its original form, but instead a neuroma, or swelling, develops around the joined axon [3].

Neuromata are typically mechano-sensitive and may be sensitive to norepinephrine and sympathetic nerve activity. Damage to the vasa nervorum causes a reduction in the blood supply to myelinated fibers, with resultant demyelination and the production of ectopic impulses [16]. In addition, peripheral nociceptors become sensitized by injury so that they have a lower threshold for firing, increase their response to noxious stimuli, and can fire in response to non-noxious stimuli.

In the acute stage, nociceptors respond to thermal and mechanical stimuli; however, when tissue damage and inflammation occur, the actions of prostanoids, bradykinin, ATP, and serotonin (5-HT) on their excitatory receptors play a major role in sensitization and activation of C-fibers [17]. Other factors such as nerve growth factor and cytokines are also important at the peripheral level, and resultant changes in the phenotype of the sensory neurons can alter their responsiveness [4].

Injury also causes changes in the Schwann cells and glia that surround axons. These are non-neuronal cells that provide support and nutrition to nerves. Furthermore, uninjured axons can spread into areas of injury, and, particularly, if

this involves central neurons, the result is the spread of pain to uninjured areas and development of "mirror" pain [3]. This contributes to the development of central sensitization and amplification of peripheral events, possibly leading to allodynia and hyperalgesia seen in patients.

From Acute to Chronic Pain

Chronic pelvic pain (CPP) is a complex condition that affects approximately 15% of women of reproductive age. In adolescents, prevalence rates of endometriosis and chronic pelvic pain are not completely clear but have previously been reported to range from 19% to 47% [18]. Nezhat et al. found, in a series of 25 females less than 21 years of age, the most common preoperative complaints were dysmenorrhea (64%) and menorrhagia (44%), followed by abnormal or irregular uterine bleeding (60%), at least 1 gastrointestinal symptom (56%), and at least 1 genitourinary symptom (52%). Additionally, 11 of the 25 (44%) adolescents reported having been to the emergency department at least 1 time because of pelvic pain. Chronic pelvic pain is responsible for 10% of gynecological specialist visits and consumes considerable amount of health resources. CPP remains an enigmatic syndrome despite all the efforts and research that have been advanced in this regard. Approximately 50% of the patients undergoing laparoscopy cannot find a reproductive cause explaining the symptomatology. That is why the orientation and management of these patients should be done from an interdisciplinary point of view involving gynecologists, pelvic pain specialists, physiatrists, psychologists, urologists, physiotherapists, nutritionists, and algesiologists, among others [18].

Although there is no definitive consensus regarding its definition, we can say that chronic pelvic pain (CPP) is the noncyclic non-oncologic pain of more than 3 months' duration that is located in the anatomical area of the pelvis, the anterior abdominal wall under the umbilicus, pelvis, perineum, genital area, lumbosacral region, or hip and that has a severity that causes functional disability and/or leads to seek medical attention. This definition precisely excludes cyclic pain/dysmenorrhea specified as pelvic pain exclusively during menses. This designation, published by ACOG since 2004, also has a very important consideration. It also says that the absence of positive clinical findings does not minimize the meaning of patients' pain. A normal physical examination does not rule out the possibility of pelvic pathology. It is more likely that patients are poorly evaluated and not that the physical examination is normal [19].

Acute pain and chronic pain are totally different not only in terms of etiology but also in terms of their course, diagnosis, treatment, and prognosis. In general, the difference between chronic and acute pain syndromes has been based on duration of symptoms. However, in terms of understanding physiopathology, the mechanism of pain is more relevant than its duration.

While acute pain is a symptom of tissue damage or an associated disease, chronic pain is in itself a disorder. Some individuals suffering from acute pain as a result of

their own conditions or of environmental effects may fall into the vicious circle leading to chronic pain and disability. Acute pain is caused by a specific disease or injury; it plays a useful biological role and is self-limiting in the majority of cases. In contrast, chronic pain must be considered as a disease in its own right. Many times, there is no evident triggering factor. When associated with a disease or tissue injury, its resolution takes longer than normal. Chronic pain does not serve any specific biological purpose and has no recognizable ending point.

Therapy for acute pain aims to treat the origin and to interrupt the transmission of nociceptive signaling. On the other hand, chronic pain therapy must be based on a multidisciplinary approach and involves more than a single therapeutic modality. Although the treatment of chronic pain often does not result in a completely pain-free condition, understanding the basis of chronic pain may lead to adequate management and significant relief. Chronic pain patients always expect complete relief of their symptoms with treatment and many times belief that their pain is attributable to an unrecognized disorder. For this reason, it is very important for healthcare providers and patients alike to understand the differences between acute and chronic pain so that management plan and outcomes can be based on realistic expectations [20].

In many chronic pain disorders, there is a weak relationship between abnormal physical findings and the intensity of pain, and, with time, it becomes nonexistent. Consequently, chronic pain is an entity with a pathophysiology of its own, its own signs and symptoms, and continues beyond the resolution of any causal disease. In many cases, it is even impossible to identify the original etiologic factor that triggered persistent pain [21].

Chronic pain is associated with multiple changes in the central and peripheral nervous systems, which contribute to the persistence of pain and make it difficult to manage. The exact mechanisms involved in the pathophysiology of pain are not fully understood. However, it is believed that both the central and the peripheral nervous systems undergo acute and long-term changes that alter the pathways of pain and end up creating lasting abnormal responses that perpetuate the symptoms [22].

Adolescents with pain for a long period of time may have activation of peripheral nociceptors by inflammatory mediators caused by endometriosis and may develop peripheral sensitization. However, this is commonly accompanied by central sensitization. It includes expanded receptive fields, increased amplitude of response to a given stimulus (hyperalgesia), pain elicited by normally innocuous stimuli (allodynia), and spontaneous pain in the absence of external stimuli. The development of allodynia and hyperalgesia may be induced by nerve injury stimulating A-beta afferents to sprout into the superficial pain transmitting areas of the dorsal horn. In this setting, visceral pain, such as dysmenorrhea, can initiate the viscerosomatic pain reflex and referred pain, resulting in chronic somatic pain and tenderness in the pelvis [23].

The development of chronic pain represents a cascade of events that are initiated at the time of peripheral stimulation or injury. The persistence of pain may be a result of plastic changes in the nervous system, both in the periphery and centrally

within the spinal cord, with or without persistence of the original stimulus. Central sensitization, once established, can clearly be maintained by ongoing peripheral activation of nociceptive afferents where a peripheral inflammatory or nociceptive stimulus persists. The balance between the descending facilitatory and inhibitory pathways is subject to change following injury, and an imbalance has been implicated in the development of chronic pain states. Serotonin, noradrenaline, and endogenous opioids are important transmitters in the descending system.

Patients with endometriosis experience increased pain intensity than controls when they receive pain stimulus outside the pelvic region. Dysfunction of the central nervous system with central hyperexcitability and central sensitization seems the likely explanation for this observation [24]. In chronic pelvic pain, clinical tests confirming sensitization include cutaneous allodynia and reduced pain thresholds primarily in the T1-L1 and S2-S4 dermatomes [25]. In a study of 181 women with chronic pelvic pain, those who demonstrated pain sensitization using these tests were more likely to report severe dysmenorrhea compared to those with no sensitization (89% vs 63%) [25, 26].

Neuropathic pain is produced by damage to or dysfunction of neurons in the peripheral or central nervous system. The potential of neuropathic pain with endometriosis is suggested by the study of Anaf et al. [27]. Endometriosis is a chronic inflammatory disease and may cause injury to the somatosensory nervous system. Injury occurs by direct infiltration of the lesion or by the production of inflammatory substances near the nerves (Fig. 10.1). As a consequence, patient may develop neuropathic pain. After nerve injury, the primary sensory afferents are involved in a complex process to induce peripheral sensitization. Nerve growth factor (NGF) is produced by endometriotic lesions, and it increases the expression of a number of mediators involved in peripheral sensitization [F].

Neuropathic pain may be peripheral or central or both. Peripheral neuropathy results from damage to cells in the peripheral nervous system, the network of the nerves, and neurons outside of the central nervous system. Some of the mechanisms that are thought to be involved in peripheral neuropathy include sensitization of nociceptors and ectopic neuronal discharges. Central neuropathic pain refers to dysfunction of the brain or spinal cord, and it is not as well defined as peripheral

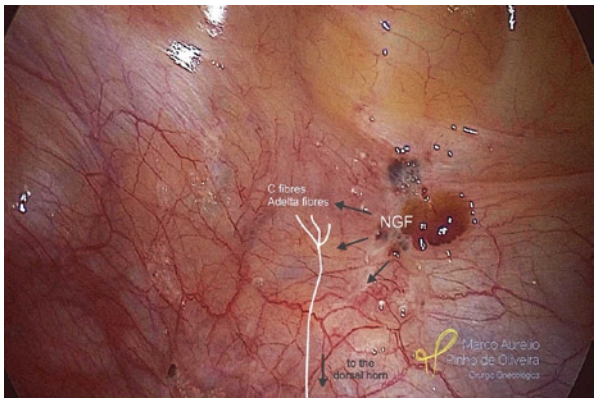

Fig. 10.1 Endometriotic lesion produces nerve growth factor (NGF) that promotes nerve proliferation and the release of inflammatory nerve sensitizers

neuropathy. The term central sensitization is used to describe the phenomena of wind-up, long-term potentiation and secondary hyperalgesia. Secondary hyperalgesia occurs in undamaged tissue adjacent to the area of actual tissue damage. It is thought to be due to an increased receptive field and reduced threshold of wide dynamic neurons in the dorsal horn. It is produced by repeated low-frequency activation of C-fibers causing a progressive increase in electrophysiological response. The N-methyl-D-aspartate (NMDA) receptor is closely involved in this sensitization process. Some of the mechanisms that are believed to be involved in central neuropathic pain include neural plasticity and central sensitization. CPP is often associated with negative cognitive, behavioral, sexual, and emotional consequences, potentially further exacerbating the pain experience [28].

Usually There Are Six Steps to the Development of CPP

Cross-Talk

Strong electrical signals originating in poorly myelinated (or non-myelinated) nerve fibers produce de novo electrical signals in the adjacent afferent fibers that are not involved in the painful stimuli.

The development of cross-talk in pelvic organs requires cross-afferent stimulus in the pelvis. The afferent information from the main pelvic organs such as the bladder, colon, rectum, and uterus is transmitted over the hypogastric, splanchnic, and pudendal nerves to cell bodies in the thoracolumbar and lumbosacral dorsal root ganglions. Typically, the prodromic afferent stimulus (from the periphery to the central nervous system) from an affected pelvic organ produces an antidromic stimulus (from the center to the periphery) as well as co-sensitization of another "uninvolved" pelvic organ. These abnormal reflex pathways may occur locally in the periphery through collateral axons (dichotomization of the afferent nerve fibers), in the spinal cord (dorsal root reflexes), and/or in the central nervous system. Consequently, the antidromic pathway may produce functional changes in another pelvic organ with little or no organic pathology [29–32].

Peripheral Sensitization

Both central (CS) and peripheral sensitization are the main causes of hypersensitivity to pain following tissue damage. Peripheral sensitization may occur in inflammatory pain, in some forms of neuropathic pain or after persistent nociceptive stimulation. Tissue damage creates dramatic changes in the chemical milieu of peripheral nociceptor endings, releasing potassium ions, substance P, bradykinin, prostaglandins, and other pro-inflammatory substances. Additionally, some intracellular contents such as adenosine triphosphate and hydrogen ions are released from the cells. In peripheral sensitization, inflammatory mediators heighten pain

perception in response to stimuli, lowering the threshold. Peripheral sensitization is associated with increased sensitivity to mechanical as well as thermal stimuli regardless of whether they are harmless (allodynia) or noxious (hyperalgesia) [21].

Central Sensitization

Central sensitization (CS) refers to an increase in the excitability of the spinal and supraspinal neuronal circuits as a result of injury or activation of the peripheral receptors. Central sensitization is a physiological phenomenon of hyperexcitability leading to neuronal dysregulation and hypersensitivity to pathological as well as harmless stimuli [32]. It appears that in CS there is a combination of a neurotransmitter-mediated disorder together with the individual's altered ability to deal with previous cognitive experiences and their impact on daily life. CS is associated with allodynia, hyperalgesia, expansion of the receptive field (with pain extending beyond the peripheral innervation area), and unusually prolonged pain after the painful stimulus has been eliminated. Generally, patients report throbbing pain, a burning sensation, tingling, or numbness.

In CS there is pain dissociation leading to an expansion of hyperalgesia beyond the site of injury and cross-hypersensitivity between several somatic and visceral structures [33, 34].

Given the implications of sensitization, it is important to bear in mind when deciding the medical management of chronic pain that somatic symptoms must be controlled and central and peripheral pain elements must also be managed [35].

Visceral-Somatic and Visceral-Visceral Convergence

There is convergence of the somatic as well as the visceral afferents on the same second-order neuron in the dorsal horn of the spinal cord. Only 2–7% of all afferent nerve fibers in each dorsal root ganglion are visceral, and dorsal horn interneurons are largely influenced by somatic fibers. For this reason, stimuli coming to the dorsal spine from the muscle, for example, are much more potent than those generated in the skin. This is why somatic pain is often reported as visceral pain, especially in the abdominal wall [36, 37]. Afferent activation of a pelvic structure influences the efferent output to another structure. Therefore, any disease or injury in one pathway may influence the abnormal activation of another pathway. This theory may explain symptom or disorder overlaps in chronic pelvic pain [38].

Spinal Cord Windup

Repeated low-frequency stimulation of C-fibers produces a gradual increase in the discharge frequency of second-order neurons in the spinal cord until they arrive at a state of almost continuous depolarization. This state results in expansion of receptive fields, permanent biochemical changes, lowering of the threshold, and, finally, sensory processing upregulation [39].

Neuroplasticity and Central Reorganization

It has been proposed that a barrage of painful stimuli to the dorsal horn may lead to cortical reorganization in patients with chronic pain. It was shown that the cortical areas where pain is represented displaced medially, possibly indicating an expansion of that representation area to neighboring areas.

The mechanisms involved in cortical reorganization in patients with chronic pain and no neuropathic damage are still unclear. It has been suggested that in the complex regional pain syndrome (CRPS) constant pain may interfere with sensory perception, not only at a cortical level but also at a subcortical and spinal level, modifying the cortical representation regions of the affected areas. For example, in patients with painful phantom limb syndrome, the increased activity of nociceptive stimuli may induce central sensitization and abnormalities in functional connectivity in the periphery and in the spinal neurons. However, it is not possible to conclude that there is always a relationship between cortical reorganization and chronic pain. Chronic pain may cause cortical reorganization, but, alternatively, maladaptive cortical reorganization may, in itself, trigger or perpetuate chronic pain [40–42].

Laparoscopic uterosacral nerve ablation to disrupt efferent nerve fibers was tested for decreasing uterine pain. However, multiple large RCTs did not find it to be beneficial in reducing endometriosis-associated pain. Cases of uterine prolapse and ureteral transection have been reported with this procedure. Presacral neurectomy, the surgical removal of the presacral plexus, has been reported 87% effective in reducing severe midline pelvic pain associated with endometriosis, particularly in patients with mild or no endometriosis. The adverse effects associated with presacral neurectomy are constipation, bladder, and urinary complaints.

Abbott et al. conducted a prospective, multicenter cohort study of 981 women with varying degrees of endometrial disease. Significant post-surgical symptom improvement over 36 months was seen in patients who underwent laparoscopic excision of endometriosis. The most notable improvement was in dysmenorrhea, with a 57% reduction; chronic pelvic pain and dyspareunia were reduced by 30%. Due to recurrent pain, a second-look surgery was performed in 9.2% of cases and histologically confirmed endometriosis recurrence was documented in 5.3% who went on to benefit from medical therapy (7.2%).

Clinical Diagnosis of Pain

Taking a Clinical History

Clinical history and the detailed physical exam are powerful tools in the final diagnosis of pain because the adequate analysis minimizes the need for unnecessary diagnostic aids and avoidable imaging studies and avoids a big number of not indicated surgeries. In addition, they play a very important therapeutic role, because they are a key piece in the proper doctor-patient relationship, generating correct expectations and allowing patients to leave the office feeling better when they are listened to and given sure expectations and clear lines of treatment. It is very important to listen to patients, allow them to tell their story, and observe emotion and affection. And, in addition, you should always be tolerant, have an open mind, and remember in patients with chronic pain, especially adolescents, that everything must be taken into account and nothing is ridiculous, impossible, or unimportant [43].

Questionnaires are a very useful tool when taking a complete and focused clinical history on patients with chronic pelvic pain. They help asking all relevant questions, without forgetting crucial issues that can sometimes be overlooked. In addition, the questionnaires allow us to address some issues that, both for patients and their doctors, may be uncomfortable during the initial visit. Therefore, it is desirable that patients with chronic pelvic pain can attend their initial consultation with the already solved questionnaire. There are several questionnaires that can be used, but a very useful instrument is the one from the International Pelvic Pain Society (www.pelvicpain.org). This validates tool is available at no cost, is in several languages, and offers great help when facing chronic pelvic pain patients at the office. The questionnaires serve in the initial approach, but never replace the direct interview, which allows, in addition to delving into specific issues, that the patient "tell her story."

In the clinical history of patients with CPP, several general and specific topics should be included:

1. General information, such as first and last names, residence address, telephone numbers, and date of birth. The full demographic information, including occupation, level of education, current employment, and type of activity performed, is fundamental in the characterization of patients and directly affects their possible diagnosis, prognosis, and treatment.
2. Allowing the patient to describe their pain, in terms of triggers, duration, what increases it, what improves it, and what things the patient believes that produces it.
3. The patient may also be asked to describe (on a visual analog pain scale from 1 to 10) the intensity of various cyclic and non-cyclic symptoms.
4. Ask about general information around pain and what kind of previous treatments patients received or tried before.

5. Use pain maps/charts of a whole-body and genital/perineal area where patients can show the location, radiation, and intensity of discomfort. The questionnaires, in general, include maps that allow patients to mark the specific sites of their symptoms.
6. It is important to always check for the history of previous surgeries. Differentiation should always be made between the procedures performed to improve the pain and any other surgical procedure to which the patient has previously submitted. Doctor should also, if possible, consult the previous surgical descriptions to know in an objective manner what procedures were performed, who performed them, and the possible complications that occurred.
7. Always ask if the patient is taking any type of medication, at what dose, since when, and under what indication. Also, ask if the medication works and if it has produced any adverse effects.
8. Ask if the painful symptoms are related to obstetric events (although not so common in adolescents) and the onset, increase, and/or persistence of symptoms. Ask about the number of pregnancies, the number of vaginal births and cesarean sections, and the date of last birth. In addition, if an episiotomy was performed during the delivery, whether there were lacerations or vaginal tears or whether an instrumented delivery was necessary.
9. Doctor needs to know if there is a relevant family history associated with CPP, including family members with previous diagnoses of endometriosis, fibromyalgia, interstitial cystitis, and irritable bowel syndrome among others.
10. Likewise, you should ask about the complete personal history, including other medical diagnoses.
11. Ask about allergies and medications. It is important to include a specific latex allergy question.
12. Include menstrual history. Ask when the first menstruation and about the frequency and regularity of the cycles. If there is dysmenorrhea and/or predysmenorrhea and for how many days. Know if there is an alteration of the menses and any received treatment for it. Also check for the family planning method used and its side effects.
13. You should ask about the patient's diet. If the patient has had an eating disorder. Also, if she has nausea or vomiting in the past. Specific questions should also be included for the diagnosis of irritable bowel syndrome, such as changes in the frequency or appearance of the stools or if the pain improves after the bowel movement.
14. Ask about health habits. If the patient smokes, exercises regularly, or consumes or has used psychoactive drugs.
15. It is very important to ask for urinary symptoms that lead provider to think about the possible diagnosis of painful bladder syndrome. In the IPPS questionnaire are included the questions of the PPUF Test (Pelvic Pain, Urgency, and Frequency), which serves as a tool both in the diagnosis and in the monitoring of painful bladder syndrome/interstitial cystitis.
16. In the initial clinical history, it is important to use scales that not only assess pain in a single plane (such as the visual analogue scale (VAS)) but also in a

multiplanar way in terms of quality of life and impact on daily roles. It is important to ask questions that assess quantitative and qualitative aspects of pain, such as effects on quality of life, temporary properties, and intensity, among others. Short form of McGill allows us not only to assess the real influence of pain in daily life but also to objectify the monitoring and response to installed management [44, 45].

The Physical Exam

A detailed and focused clinical examination allows an objective and systematic pain mapping. The physical examination in patients with chronic pelvic pain seeks fundamentally to replicate the exact location of the pain and to look for specific causes according to the data previously obtained in the anamnesis [46].

A practical way to face the physical examination in patients with chronic pelvic pain is to divide it in four components ("the four S").

1. First component: *Standing* exam

   With the patient standing, the examiner should explore a variety of findings.

   - The general appearance should always be considered as a very important clinical marker of the systemic impact of the disease.
   - Gait and posture must also be evaluated. Remember that patients with chronic pelvic pain often have a characteristic, antalgic gait. In addition, these patients usually have a distinctive posture, where the thoracic kyphosis and lumbar lordosis are accentuated and there is a displacement of the pelvis and the line of gravity of the knees to the anterior.
   - A discrepancy in the length of the lower limbs should always be sought. This difference is significant when there is a disparity of more than 10 mm between one limb and another, measured from both iliac crests.
   - The presence of pain in the pubic symphysis should be evaluated. This is a relatively frequent and overlooked finding in many patients, especially those with an obstetric history.
   - Fibromyalgia is a common comorbidity in all conditions of chronic pain, including pelvic pain. For that reason, it is important to evaluate certain findings during the physical examination. The presence of pain in the 4 quadrants of the body of more than 3 months associated with 11 of 18 specific painful points of the anatomy should make consider the fibromyalgia as an associated pain generator. The palpation is performed with a single finger and exerting a pressure of 4 kg/cm^2 (or what is the same, until the tip of the examiner finger is white with pressure).
   - Ask patients to lean forward and backward. When leaning forward, you should evaluate if pain occurs, the presence or reversion of lumbar lordosis, and range of motion. When leaning backward, look for the range of motion,

for the presence of lumbar pain, and if "myofascial jump" occurs when the patient refers abdominal pain with this movement.
- Also look for lumbar sacral pain, sacroiliac dysfunction, and pelvic rotation.

2. Second component: Sitting exam

- During the physical examination of the seated patient, the posture should be evaluated. Throughout the anamnesis, it is possible to observe how the patient feels, the changes in posture, the presence of asymmetries if the patient sits or leans on one or both of the backsides, and, possibly, the lower limb discrepancy or scoliosis.
- Additionally, a neurological evaluation could be performed. It is not required to do it in all cases, but it must be considered in complex cases. For this evaluation, flexion-extension of the knee should be reviewed, evaluating L5-S1 and L3-L4, respectively; inversion and eversion of the ankle, examining L4 and L5-S1, respectively; and the dorsal (LL4-L5) and plantar flexion of the foot (S1-S2).
- Finally, an evaluation of the general condition of the patient must be performed.

3. Third component: Supine examination

- With the patient in a supine position, a general inspection should be performed, evaluating the presence of scars from previous surgeries on the abdominal wall and changes in skin color; assess the presence of masses and abdominal pain both with superficial and deep palpation.
- Always look for abdominal trigger points. For this, one should perform superficial palpation of 1–3 seconds, with the tip of a single finger, until it turns white, corresponding to a pressure of around 4 kg/cm^2. Perform a systematic evaluation of the entire abdomen according to the distribution of the dermatomes. The total or partial reproduction of painful symptoms on palpation must be evaluated.
- In 1926, the Carnett test was described in order to differentiate whether the patient presents intra-abdominal visceral pain or abdominal wall myofascial pain. While palpating the tender point, doctor asks the patient to raise the head or legs, making the abdominal muscles tense. If the pain increases, it suggests a myofascial origin. If the pain does not change or decrease, it suggests an intra-abdominal origin of the pain [47].
- On the other hand, it is important to assess the presence of ovarian points. Pressure is applied for 3–5 seconds, at the junction of the medial third with the two lateral thirds of an imaginary line drawn between the umbilicus and the anterior superior iliac crest. When applying this pressure, a reproduction of the symptoms can occur. In conjunction with symptoms, positive ovarian points can lead to think about the diagnosis of pelvic congestion in certain patients with chronic pelvic pain [43].
- The physical examination should rule out the presence of incisional, femoral, and inguinal hernias, performing palpation of the inguinal area and the abdominal wall with and without Valsalva maneuvers.

- We must take into account the presence of previous abdominal scars including the ports of laparoscopic surgery, since they can be related to neural entrapment and peripheral neuropathy, showing symptoms such as allodynia, hypoesthesia, anesthesia, or burning sensation. Ilioinguinal and iliohypogastric (II-IH) neuropathy is a very common condition in patients with chronic pelvic pain, above all those who have had previous abdominal incisions (including laparoscopic ports). Therefore, it is very important to assess the presence of this neuropathy examining the territory of the nerves. The II-IH triangle should be assessed with the help of a Q-tip, evaluating the changes in the sensitivity of the abdominal wall.
- Finally, the clinical signs indicating radiculopathy can be evaluated, such as the sign of Lasége. While the patient is in the supine position, elevation of the lower limb is performed in extension. This test is positive when the patient presents pain along the distribution of the lumbar roots. This pain is caused by the stretching of the lower lumbar and sacral roots when the leg is flexed. This sign is positive if the angle at which the pain is caused is <45°.

4. Fourth component: *Stirrups*

- With the patient in a lithotomy position, a general inspection should be performed in search of areas of erythema, secretions, ulcers, changes in skin color, infections, fistulas, traumas, or fissures.
- The Q-tip test should be performed in search of vulvar pain, sensibility changes, or peripheral neuropathies. For this, the labia majora should be separated manually, and then, with a Q-tip, eight points are gently palpated distributed in the vestibule, the hymen, and the area of the minor vestibular glands.
- The pinprick test is one of the most important diagnostic tests to assess the presence of pudendal neuralgia. To evaluate the three terminal branches of this nerve on each side is simple and fast. For this test, the dermal sensation of the vulva is compared with the medial aspect of the thigh. The asymmetric changes are more specific [43, 48].
- On the other hand, pelvic muscle tones should always be evaluated. The examination must be done with only one finger, clockwise, taking into account the muscle tone, presence of muscular fibrous bands, the presence of trigger points, and the reproduction of the symptoms. Various pelvic muscle groups must be evaluated including pubococcygeal, iliococcygeal, and obturator on each side. Patients with myofascial syndrome/myalgia due to pelvic floor tension will experience pain with palpation.
- Valleix phenomenon occurs when performing percussion on the pudendal canal, which is medial to the ischial spine. This pressure reproduces the symptoms. The pain can be radiated to the perineal region, vulva, lower abdomen, buttocks, and lower limbs.
- Evaluating the urethra, the bladder trigone, and the bladder, a palpation should be made on the anterior vaginal wall, looking for areas of induration, thickening, or pain reproduction (on the bladder base). The normal reaction presented

by the patient is urinary urgency. The presence of pain should be correlated with the history for suspected painful bladder syndrome/interstitial cystitis [49].

- Finally, if the adolescent has already had sexual intercourse, the physical examination should be completed with cervical vaginoscopy, excluding cervical pathology, infections, or polyps. Traditional bimanual vaginal examination can be performed to evaluate the uterus, cul-de-sac, and adnexa. Digital rectal examination is not mandatory but is especially useful in girls with intact hymen and also to evaluate the recto-vaginal septum and the anal sphincter.

Conclusion

Adolescent endometriosis is not infrequent, but its exact prevalence remains unknown. Pelvic pain is very common in this group of patients. The diagnosis is often delayed, leading to suffering for several years, so there is a need for early diagnosis of endometriosis in adolescents with pain. This could, hopefully, avoid the progression from acute to chronic pelvic pain, with its associated problems such as peripheric and central sensitization, converting nociceptive to neuropathic pain. Treatment usually is a combination of surgery with complete excision of the lesions and postoperative hormonal treatment, but long-term pain recurrence remains a significant problem. Gynecologists must be aware of how to diagnose and treat neuropathic pain, preferably via a multidisciplinary approach.

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Chapter 11
Reproductive Tract Anomalies in Adolescent Endometriosis

Tierney Wolgemuth and Joseph Sanfilippo

Introduction

Congenital abnormalities of the female reproductive tract, including Müllerian anomalies, comprise a varied group of disorders, which include abnormal sexual development and disorders of internal and external genitalia. As primary amenorrhea is a common presenting symptom, these conditions are frequently diagnosed during early- or mid-adolescence.

Reproductive tract anomalies are clinically important due to symptomatology that impacts the patient's quality of life and fertility potential. Obstructive anomalies typically present with amenorrhea or cyclic pelvic pain due to obstructive menstruation without external bleeding. This obstructed outflow tract is highly associated with endometriosis, theoretically via retrograde menstruation or coelomic metaplasia mechanisms as discussed in other chapters.

This chapter discusses the common presentations, diagnosis, and management of the reproductive tract anomalies in adolescents and discusses the relationship of such with endometriosis.

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Embryology

The female reproductive organs consist of external genitalia, gonads, and an internal duct system, that is, the Müllerian ducts. Development of the reproductive, urinary, and distal gastrointestinal tracts is closely related; thus, knowledge of embryology is critical to the understanding, diagnosis, and treatment of genital malformations and their associations with gastrointestinal and genitourinary anomalies (Table 11.1).

An embryo's gender is determined genetically by sex chromosomes. Testicular differentiation is partly induced by the SRY gene on the Y chromosome, and the testes then produce AMH which prevents female ductal development. Alternatively, female development occurs in presence of two X chromosomes with the influence of several genes, including *Wnt4* [1]. The primordial germ cells derive from peritoneal mesothelial thickening and subsequently migrate to the gonadal ridge during early development. These primordial germ cells differentiate into ovaries or testes around 7 weeks of development. Differentiation of female ductal system is not dependent on ovarian development.

In the presence of AMH, the Müllerian ducts appear as invaginations of the dorsal coelomic epithelium lateral to each Wolffian duct at week 5. Each Müllerian duct begins as a solid bud which elongates and gradually canalizes to form a luminal structure. The paired ducts continue to grow medially and caudally until they meet and become fused at the urogenital septum. Correct development of the female reproductive tract requires both fusion of the bilateral Müllerian ducts and resorption of the resulting uterine septum to form a single uterovaginal canal. The most cranial parts of the Müllerian ducts remain separate and form the fallopian tubes while the caudal segments of the Müllerian ducts join to form the uterus and upper vagina. The lower vagina is formed by the urogenital sinus, which joins with the Müllerian ducts at the Müllerian tubercle. The sinovaginal bulbs, which are formed

Table 11.1 Summary of reproductive tract development

Gestational age (weeks)	Developmental stage
6	External and internal genital structures begin to form, and common Müllerian and Wolffian systems exist
7	Differentiation of primitive gonads
9	Urogenital sinus develops and lack of exposure to androgens allows regression of Wolffian ducts and further Müllerian development
12–14	Müllerian ducts fuse with urogenital sinus
15–26	Cephalic growth of sinovaginal bulb occurs
15–26	After cephalic growth, fusion of sinovaginal bulb will form vaginal plate; subsequently, canalization of the vagina occurs
20	Stromal cells of the Müllerian ducts condense to form the cervix

Modified from Dietrich et al., Obstructive Reproductive Tract Anomalies. In Journal of Pediatric and Adolescent Gynecology; 2018

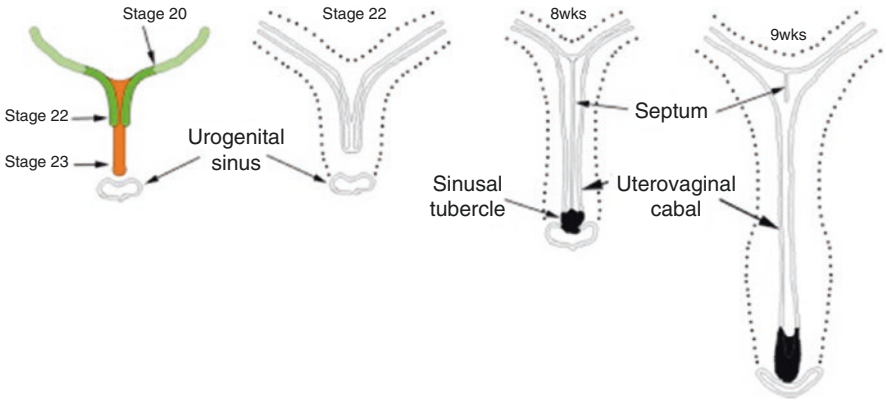

Fig. 11.1 Summary of reproductive tract development. In (**a**), Mullerian duct caudal extension is depicted at Carnegie stages 20–23 (50–56 days). (**b**–**d**) depict fusion of the bilateral Mullerian Ducts to form the uterovaginal canal, septum formation, and subsequent septum disappearance. ([Modified from Robboy et al. New insights into human female reproductive tract development. In Differentiation; 2017)

by endodermal evaginations, and the vaginal cord, which is derived from cellular proliferation of the lower Müllerian ducts, combine to form the vaginal plate [2]. Around week 20, stromal cells of the fused Müllerian ducts condense to form the cervix. Likewise, the mesenchyme surrounding the ducts becomes condensed to form the musculature of the female genital tracts (Fig. 11.1) [3].

The hymen, which is not derived from the Müllerian ducts, is a thin septum separating the vaginal lumen above from the urogenital sinus below. Although the central portion usually degenerates before birth, a thin fold of membrane may persist at the vaginal introitus in a variety of shapes and configurations.

The external genitalia is formed when the mesoderm around the cloacal membrane forms the genital tubercle with urogenital folds and labioscrotal swellings on either side [4]. In the presence of estrogen, the genital tubercle forms the clitoris; the urogenital folds form the labia minora; and the labioscrotal swellings form the labia majora and mons pubis. Any increase in androgens will cause masculinization of the external genitalia in females.

The urogenital system develops concurrently and in close proximity to the reproductive system, which in part explains the common association of renal and reproductive tract malformations. Early in development, intermediate mesoderm extends posteriorly along the length of the embryo to form the urogenital ridges, which then divides to form the nephrogenic and genital ridges. The nephrogenic ridge gives rise to the early mesonephric kidneys and is connected to the Wolffian ducts by the cloaca (which is the common opening to embryologic genital, urinary, and alimentary tracts) [2]. At 5 weeks, the ureteric bud forms as an outgrowth of the Wolffian duct and eventually forms the functional kidney. At 7 weeks, the urorectal septum divides the cloaca into the urogenital sinus and the rectum. Finally, the urogenital sinus divides to form the bladder, urethra, and distal vagina [4].

Overview of Reproductive Tract Anomalies

Classification

The simplest and perhaps most commonly used classification of uterine anomalies was developed by the American Society of Reproductive Medicine (ASRM, formerly the American Fertility Society) and is based on uterine anatomy and its relationship to fertility [5] (Fig. 11.2). However, this system fails to accommodate complex anomalies, particularly those involving the vagina and cervix. Consequently, another system ["Congenital Uterine Anomalies" (CONUTA)] was developed by the European Society of Human Reproduction and Embryology (ESHRE) to more fully address the complexities and variations in these conditions (Fig. 11.3) [5]. This system provides more precision by categorizing anomalies descriptively based on structure of the corpus, cervix, and vagina. Although the CONUTA system includes anomalies of non-Müllerian origin, it still does not cover all possible variations. Thus, other researchers have suggested classification via embryologic origin due to close relationship of renal and Müllerian anomalies [6]. Proponents of embryological-based systems suggest that Müllerian abnormalities may be the result of complex malformations in the Wolffian (mesonephric) system or the gubernaculum and thus should be classified accordingly.

Incidence and Prevalence

Though incidence is difficult to determine, estimates run 0.5–5% in the general population with increased frequency among those with infertility [7–9]. Other studies report higher prevalence, with abnormalities in up to 6.7% of women in the

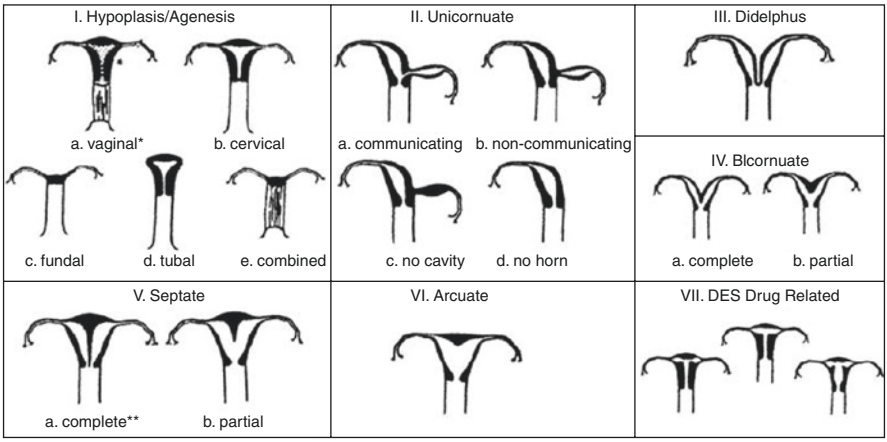

Fig. 11.2 ASRM classification of Mullerian anomalies. (Presented with permission from the Chandler TM. Mullerian duct anomalies: from diagnosis to intervention. In The British Journal of Radiology; 2009, p 1035.87)

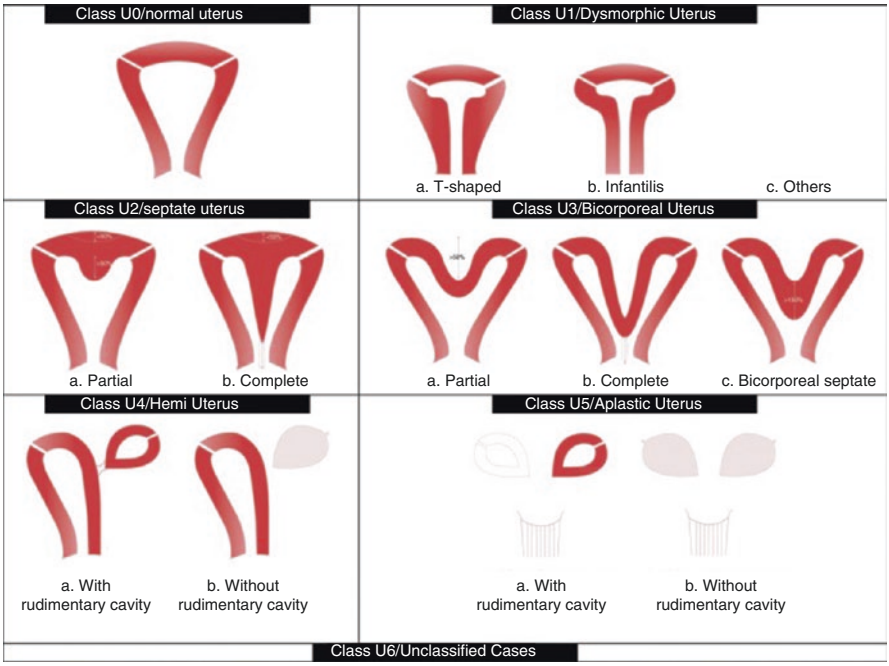

Fig. 11.3 The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. (Presented with permission from Grimbizis et al. The ESHRE–ESGE consensus on the classification of female genital tract congenital anomalies. In Hum Reprod; 2013)

general population, 7.3% of women with infertility, and 16.7% of women with recurrent miscarriage [10]. The frequency of these anomalies using ASRM classification is: Class V (35%), Class IV (26%), Class VI (18%), Class II (10%), Class III (8%), and Class I (3%), although rates vary within the literature [9].

Presentation

Although these conditions are frequently asymptomatic, some patients present with dyspareunia and menstrual abnormalities such as amenorrhea, dysmenorrhea, abnormal uterine bleeding, and pelvic pain. For patients with complete uterine or vaginal agenesis, primary amenorrhea often prompts presentation within several years of missed menarche. In patients who are able to achieve pregnancy, obstetric complications include spontaneous abortion, recurrent pregnancy loss, preterm labor, intrauterine growth restriction, and abnormal fetal presentations [11, 12].

Diagnosis

In patients with suspected reproductive tract anomalies, a thorough history includes symptoms of pelvic pain or bleeding and sexual history, including attempts at sexual intercourse. On exam, patients will have normal breast development, body hair, and genitalia. The vagina may appear as a small flush dimple or a longer canal with no cervix at the apex in patients whose anomaly includes vaginal atresia. Initial evaluation should include serum testosterone and FSH, as well as a karyotype to differentiate from androgen insensitivity disorder. Patients with reproductive tract anomalies will have a normal 46XX karyotype and female endocrine profile [13].

For initial imaging, hysterosalpingography assesses internal uterine contour and standard 2D ultrasonography allows imaging of the adnexa and kidneys, though it provides little information about uterine contour. MRI and 3D ultrasonography are thus superior noninvasive tools and preferred for definitive diagnosis [11]. 3D ultrasonography sensitivity in identifying abnormal uteri approaches 100% and accuracy of diagnosing the exact anomaly ranges from 88% to 100% [14–17]. As studies indicate a high level of agreement between 3D ultrasonography and MRI in the diagnosis of uterine anomalies, either is an acceptable confirmatory modality [17–19]. For better lower pelvis definition and to assess endometrial activity, MRI interpreted by a radiologist with expertise in reproductive anomalies is ideal [20]. If needed, additional diagnostic information may be obtained via exam under anesthesia, vaginoscopy in the office or operating room, or hysteroscopy. Laparoscopy is not necessary to diagnose these anomalies but may be helpful in women with pelvic pain and suspected endometriosis. Given high rates of concomitant renal and skeletal anomaly, all women diagnosed with genital anomaly should undergo evaluation for associated abnormalities with ultrasound or alternate imaging modality.

Theories of Endometriosis in Patients with Reproductive Tract Anomalies

As discussed in prior chapters, retrograde menstruation is among the most popular theories of endometriosis. Many researchers suggest immune system alteration is also required for implantation and growth of refluxed endometrium such that endometriosis implants result from deficient lymphotoxic response to endometrial antigens [21, 22]. Thus, proponents of this theory purport that the extent of endometriosis is due to both the volume of reflux and the relative ability of the immune system to clear refluxed material.

Support for retrograde menstruation includes evidence that endometriosis is not more frequent in patients with reproductive tract anomalies overall but is more frequent in those with outflow obstruction, hematosalpinx, hematometra, or hematocolpos [23–25]. Although reported rates vary, Dovey and Sanfilippo have estimated the incidence of endometriosis in adolescents with genital tract anomalies varies

between 11 and 40.2% [26]. Presence of outflow obstruction also impacts disease severity such that in the presence of genital tract malformations the onset of the disease occurred earlier than in girls without anomalies (16.2 versus 19.0 years) [27]. The role of outflow obstruction may be particularly salient in endometriosis presenting in children and young adolescents, as occult vaginal bleeding occurs in most neonates but overt bleeding is prevented by functional "plugging" of the endocervical canal. Thus, implants in younger patients may originate from retrograde uterine bleeding soon after birth [28].

The theory of retrograde menstruation is further supported by anatomic distribution of endometrial implants, which is affected by gravity, uterine position, and pelvic cell type (simple cuboidal is more hospitable to implants than stratified squamous) encountered [29]. This association between obstruction and anatomic placement of endometriosis has been confirmed in women with obstructed hemivagina, who more commonly have implants ipsilateral to the obstructive vagina [30]. Similarly, a recent study of women with obstructive anomalies found that only patients with functioning endometrium developed endometriosis [23].

Other theories to explain the association of endometriosis with uterine malformations suggest that implants may result not from reflux, but rather from developmental defects of differentiation or migration of the Müllerian duct system during embryogenesis. This theory has gained traction in recent years, as genetic and epigenetic studies have demonstrated significant differences in tissues and cell types that comprise endometrial implants compared to native endometrial tissues [31]. However, due to the anatomic distribution of implants discussed above, as well as the increased rates of endometriosis among women with obstructive anomalies, retrograde menstruation remains the most prominent theory of pathogenesis [25, 29].

Agenesis

Müllerian Agenesis

Incidence and Etiology

Classic Müllerian agenesis is also known as Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome (ASRM Class I) and is found in 1 per 4000–5000 females [32, 33]. This anomaly involves congenital absence of the uterus, cervix, and upper vagina due to failure of the lower portion of the Müllerian ducts to develop. Patients will often have a shallow vaginal pouch as the lower vagina develops from the vaginal plate rather than the Müllerian ducts. The upper Müllerian ducts usually develop normally, thus fallopian tubes are often present. Likewise, patients have normal ovaries as gonads derive from another embryologic source.

Müllerian agenesis is due to errors of normal embryologic development influenced by genetic mutations, hormonal abnormalities, and environmental insults. Although many studies have sought to characterize genetic causes of Müllerian

agenesis, only the *Wnt4* gene has thus far been implicated [34]. Rather, most cases are sporadic with few reports of familial occurrence inherited in an autosomal dominant pattern with variable penetrance and expressivity [11]. Likewise, besides DES exposure, specific environmental insults have yet to be established.

Müllerian anomalies exist on a spectrum, and approximately 90% of affected women will have some degree of Müllerian development, and some may have remnant endometrial tissues [35]. This rudimentary endometrium is active in 2–7% of cases [20].

Presentation

Complete Müllerian agenesis is the second most common cause of primary amenorrhea behind gonadal dysgenesis and often presents between ages 14 and 17 [36]. Patients are genetically and phenotypically normal and exam reveals normal secondary sex characteristics including normal breast development, axillary and pubic hair, and external genitalia. However, the vagina is absent or presents as a dimple, short pouch, or blinded structure without a cervix. Patients with active rudimentary endometrium may experience cyclic abdominal pain due to hematocolpos, hematometra, or endometriosis. Other patients may present with pain or difficulty with intercourse.

Associations

Due to close anatomic proximity and embryologic origin, renal malformations occur in ~25–50% of patients with Müllerian agenesis [37–39]. These anomalies include unilateral renal agenesis, pelvic or horseshoe kidney, hydronephrosis, or irregularities of the conducting system. Skeletal malformations occur in 10–15% of patients and may involve the spine, ribs, or extremities [40]. Malformations of urinary, cardiac, and skeletal (MURCS) syndrome—a variant of Müllerian agenesis involving renal, skeletal, and cardiac malformations—is observed in up to 12% of MRKH patients [34, 40]. Müllerian agenesis is also associated with VACTRL by an unknown mechanism.

Diagnosis

Diagnosis of Müllerian agenesis must include differentiation from obstructive congenital anomalies such as low transverse vaginal septum and imperforate hymen. As the uterus and vagina are present in these conditions, ultrasound is used to distinguish these diagnoses. The clinician must also differentiate from 46XY conditions such as androgen insensitivity syndrome (AIS), which features elevated serum testosterone compared to normal female levels in Müllerian agenesis and lack axillary or pubic hair. Imaging to confirm presence and classification of Müllerian anomaly is described above.

Management

In patients experiencing pain due to active endometrium, functional uterine horns should be excised to prevent or treat hematocolpos, hematometra, and endometriosis. For women whose Müllerian anomaly includes vaginal agenesis, mechanical elongation and dilation are the first-line approach to enable comfortable vaginal intercourse. As the perineum is embryologically pliable, daily increasing external pressure can create a neocavity over time. This sequential vaginal dilation therapy employs the patient's use of graduated Lucite dilators of progressively increasing diameter to create a functional vagina [41]. Although this method requires patient adherence and maturity to complete, it is successful in nearly 95% of women [42]. The patient should determine when she is ready to proceed, usually in preparation for coitarche. Most women report the process to be comfortable and relatively easy, although treatment is time consuming and requires at least 2 hours of dilation daily [43]. Complications are uncommon but include urethritis, cystitis, vaginal apex necrosis, fistulas, and secondary prolapse [44]. Failure is most often due to noncompliance, although nonadherence to primary dilation therapy is not harmful and patients can always proceed again in the future.

Various methods of surgical neovagina formation are possible for women who fail primary dilation or prefer surgical treatment. Minimally invasive technological innovation has provided surgeons with several techniques for management, the details of which are summarized in Table 11.2 [44]. Surgical approach does not avoid dilation therapy, and most women will need to have frequent intercourse or use dilators to ensure maintenance of vaginal patency and length. Patients choosing surgical management should be referred to a center of expertise for this care.

Complications of surgical neovagina formation include injury to bowel, bladder, and urethra; vesicovaginal, urethrovaginal, or rectovaginal fistula formation; and surgical bleeding. Likewise, stricture and contracture due to scarring and formation of granulation tissue can occur. Reduced vaginal length is likely in settings of poor compliance with use of molds and/or coitus. However, the overall incidence of complications is low and in general less than 10% [45].

Psychosocial support is a key aspect of managing Müllerian agenesis, as adolescents may grieve the loss of their fertility and question their female identity [46]. Counseling and participation in support groups can reduce these psychological symptoms, and providers should be prepared to offer guidance on disclosing their condition to peers and romantic partners [47]. Patients should also be counseled on options for future fertility including adoption and in vitro fertilization (IVF) with gestational surrogacy [48]. Uterine transplants have also been done but are not widely available [49]. Although most adolescents with Müllerian agenesis are not at risk for pregnancy, they should be counseled on the importance of using barrier protection against STIs and receive standard HPV immunization.

As the diagnosis of Müllerian agenesis is typically difficult for patients, temporary endometrial suppression may allow time for individuals to receive psychosocial support and education about the diagnosis [50]. Suppression is achieved with combined estrogen and progestin hormonal contraception, that is, oral contraceptive pills, progestin only therapy, or gonadotropin releasing hormone agonist-antagonist

Table 11.2 Surgical therapies for vaginal agenesis

Surgical procedure	Method	Advantages	Disadvantages	Penetrative sex (%)	Time to sexual activity
McIndoe/ Abbe Vaginoplasty	Perineal dissection of neovaginal space uses a split-thickness skin graft or alternative graft material	Avoid initial self-dilation	Need for absolute patient compliance with post-op stenting Requires 6 months of post-op dilation Significant rate of post-op stenosis Neovaginal complications related to graft type used Lubrication problems	75.8	4–6 months
Vecchietti Vaginoplasty	Traction device is attached to the abdominal wall and a stent in vaginal dimple. Wires are shortened daily to increase stent depth	Avoid initial self-dilation Early possibility of coitus	Hospitalization for 7–8 days Requires post-op dilation Possibility of surgical complications	83.8	49.8 days
Davydov Vaginoplasty	Modification of the McIndoe vaginoplasty uses Laparoscopically mobilized pelvic peritoneum to line the Neovaginal space	Avoid initial self-dilation	Same as for McIndoe/Abbe with increased possibility of surgical complications	81.5	N/A
Intestinal vaginoplasty	Most commonly, sigmoid colon is mobilized on a vascular pedicle and transposed Into the pelvis as a neovagina. It is sutured in place to the introitus	Possible for patients who have been unsuccessful with other methods and have scarring of recto-vesicular space No lubrication problems No post-op stenting	Higher morbidity of bowel surgery Management of mucous production by intestinal neovaginal May need post-op dilation if introital stenosis	86.3	4.3 months

Modified from McQuillan and Grover, Systematic review of sexual function and satisfactionfollowing the management of vaginal agenesis. Int Urogynecol J. https://doi.org/10.1007/s00192-013-2316-3

injections or oral with add-back therapy if long-term treatment is prescribed. Surgery is indicated if suppression does not adequately control symptoms or for confirmative diagnosis with concomitant suppressive therapy when indicated.

Vaginal Atresia

Etiology and Incidence

Vaginal atresia occurs when the urogenital sinus fails to form the lower portion of the vagina. The uterus, cervix, and upper vagina develop normally, and there is a space occupied by areolar type fibrous tissue between the obstructed vagina and the area of the normal introitus [51]. It may present as a component of Mullerian agenesis or occur in isolation. Complete vaginal atresia occurs in 1 per 4000 to 1 per 10,000 females [52].

Presentation

As vaginal atresia invariably leads to outflow obstruction, primary amenorrhea is the most commonly presenting symptom. Patients may develop cyclic or chronic pain and a pelvic or abdominal mass as the upper vagina fills with cervical mucus or blood after concealed menarche. This may result in severe pain after only a few months of obstructed flow [53].

Diagnosis

In these patients, the vagina is present at a distance much higher above the perineum (Fig. 11.4]. Thus, on exam the vagina is nonpatent and appears as a small dimple. In some patients, an abdominal mass can be palpated. A rectoabdominal examination may be helpful to determine the presence of midline structures, such as distention of the upper vagina or uterus. Normal secondary development is observed. If exam is suggestive of vaginal atresia, the diagnosis is made definitively with pelvic ultrasonography and abdominal MRI [50, 53]. MRI yields the additional benefit of allowing exclusion of the diagnosis of cervical agenesis or associated urinary system anomalies [54].

Management

First-line management involves surgical repair followed by prolonged use of silicone dilators to prevent scarring or constriction. The premise of this surgery is to connect the lower vagina to the upper vagina with removal of intervening

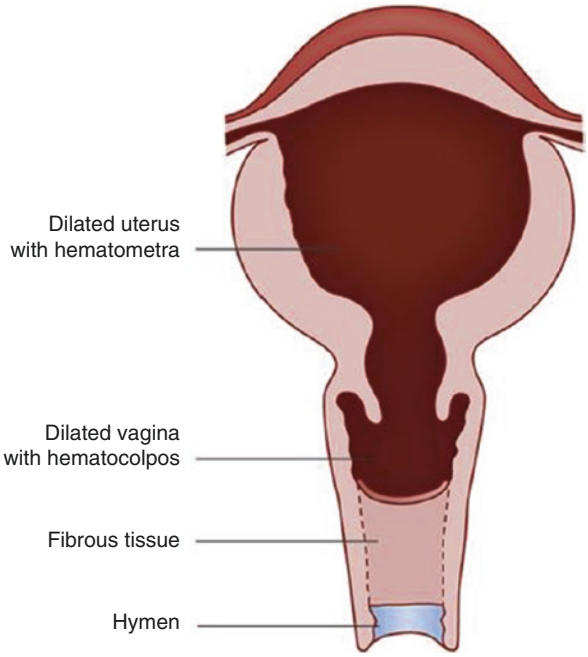

Fig. 11.4 Lower vaginal atresia. (Presented with permission from Dietrich et al. Obstructive Reproductive Tract Anomalies. In J Ped Adol Gyn; 2014)

obstructive tissue [51]. Care should be taken to avoid the urethra, bladder, and rectum. Using a perineal approach, the vagina can be entered to drain the obstruction and expose normal vaginal epithelium above. The upper vagina is then joined to the lower vaginal dimple using a pullthrough procedure. If the distance to the vagina is too great and the vagina will not reach the introitus, grafts have been used to join the upper vagina and the introitus. However, this procedure requires a combined abdominal and perineal approach and is better completed during early childhood.

As with Müllerian agenesis, some patients may opt to delay definitive surgical correction with suppression of endometrial activity [55]. Alternative approaches to delaying surgical repair include using needle drainage of obstructed menstrual products, continuous oral contraceptives to suppress re-accumulation of hematocolpos, and vaginal dilation to lengthen the lower vaginal segment and facilitate later repair and anastomosis [56].

Agenesis and Endometriosis

As previously discussed, many women with Müllerian or vaginal agenesis have endometrial remnants. One study of patients with MRKH found that 48% had uterine remnants and that 39% of remnants contained endometrium. The presence of

endometrial remnants is significantly associated with pelvic pain and endometriosis in these patients [57]. Other studies have found even higher prevalence of remnant uterine tissue, with endometrium evident in up to 84% of patients with MRKH [23, 58, 59]. However, remnant endometrial tissue is not necessary for the development of endometriosis in MRKH, as endometriosis has been reported in patients who do not have functioning endometrial tissue [60, 61]. Thus, we recommend MRI evaluation in all patients with MRKH who present with pelvic pain [57]. Definitive management of pelvic pain in patients with MRKH involves removal of functional endometrium.

Other Obstructive Anomalies

Imperforate Hymen

Etiology and Incidence

Imperforate hymen results from failed resorption of the hymenal septum that separates the sinovaginal bulbs from the urogenital sinus below. It is the most common obstructive anomaly and occurs in 1 per every 2000 females [50].

Presentation

In patients with imperforate hymen, menstruation causes a distended vagina that becomes enlarged and painful after several bleeding episodes. The patient may also present with urinary retention, bowel complaints, or a palpable abdominal mass. As discussed above, maternal estrogen may stimulate uterovaginal secretions and cause hydrometrocolpos in newborns, rarely leading to renal failure in these young infants [62].

Diagnosis

Visual inspection of the vulva will show no hymenal opening and usually reveals a bulging or bluish hymenal membrane, though exam may be limited by patient discomfort (Fig. 11.5) [63]. Rectal examination is usually tolerated and reveals a bulge just inside the anal sphincter. If no bulge is appreciated, obtain diagnostic imaging including pelvic or translabial ultrasonography. However, imaging is not necessary if diagnosis is confirmed visually and by rectal exam [50, 54].

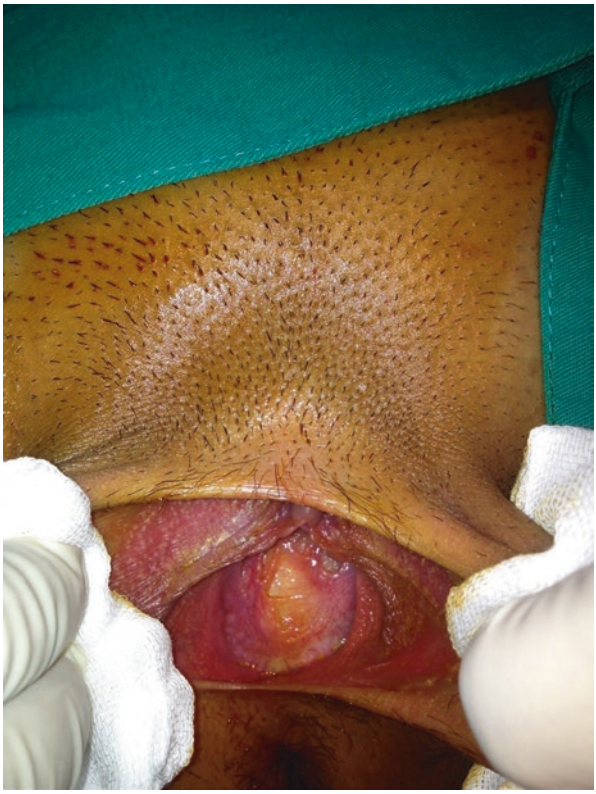

Fig. 11.5 Imperforate hymen. (Presented with permission from Cetin et al. Annular Hymenotomy for Imperforate Hymen. In J Obstet Gyn Research; 2016)

Management

Imperforate hymen is managed surgically in an urgent fashion via excision of hymenal tissue and suctioning of menstrual contents. Unlike vaginal atresia, there is no risk of stenosis, and postoperative dilation is not required. Early diagnosis is key to reduce morbidity associated with the condition. Incorporating examination of the external genitalia into routine practice can enable diagnosis before symptoms develop, or alternate imaging becomes necessary [64].

Transverse Vaginal Septum

Background and Incidence

Transverse vaginal septa are congenital horizontal partitions within the vagina resulting from failed fusion of the caudal portion of the Müllerian ducts or failed canalization of the vaginal plate. These anomalies are rare and occur in 1 per 30,000 females [65]. Septa are typically bands of thick fibrous tissue that run across an

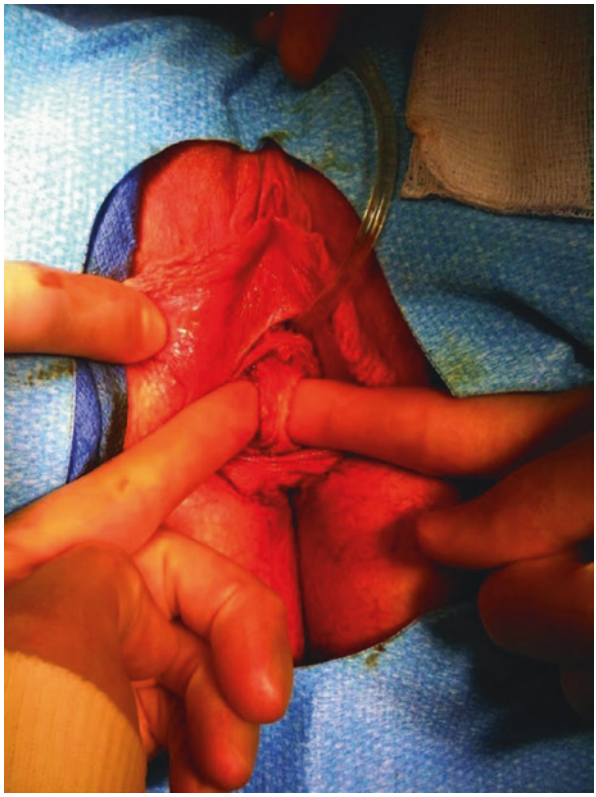

Fig. 11.6 Transverse vaginal septa. (Presented with permission from Lankford et al. Congenital Reproductive Abnormalities. In J Midwifery Womens Health; 2013)

otherwise normal vagina (Fig. 11.6) [66]. Transverse septum may be found low (14%), mid (40%), or high (46%) in the vaginal canal, and vaginal depth ranges from 1 cm to 8 cm depending on level of obstruction (Fig. 11.7) [67, 68]. Septum thickness varies but is usually about 1 cm, with thicker septa occurring near cervix. Septa may be obstructive, but are more commonly perforate (61%), often having small fenestrations that allow passage of some menstrual products [69].

Presentation

Obstructive septa present as primary amenorrhea and/or cyclic abdominal pain at menarche. These patients present similarly to an imperforate hymen, with episodes of abdominal pain of increasing severity. Patients may also present with dyspareunia or a fluid collection that is large enough to compress abdominal organs and cause discomfort.

Patients with partially obstructive septa may initially have normal menstrual flow but late develop symptoms of obstruction as menstrual contents accumulate [70]. Ascending infection through fenestrations may cause pyocolpos and pyometra,

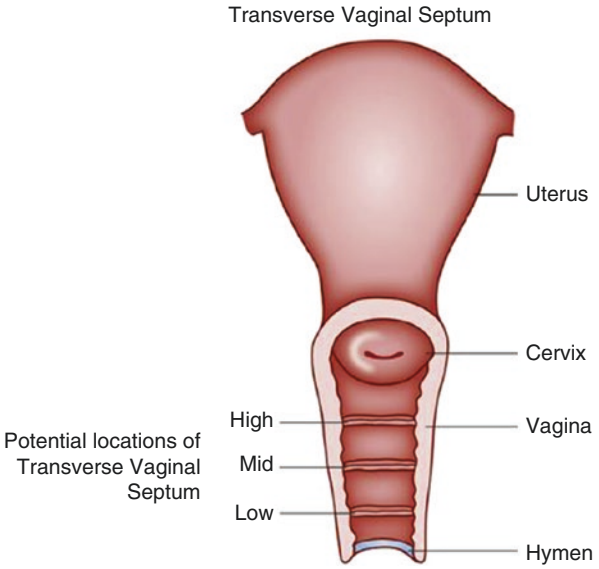

Fig. 11.7 Possible locations of transverse vaginal septa. (Presented with permission from Dietrich et al. Obstructive Reproductive Tract Anomalies. In J Ped Adol Gyn; 2014)

resulting in foul-smelling vaginal discharge, fever, and abdominal pain [50]. Transverse vaginal septa are rarely associated with urologic abnormality, bicornate uterus, coarctation of aorta, and spinal malformation [11].

Diagnosis

On exam, the vulva and external genitalia are normal, though pelvic exam reveals a short, blind-ended vagina with inability to visualize the cervix. Unlike an imperforate hymen, no bulging membrane will be visible at the introitus. Examine both the vagina and rectum to assess caudal aspect of the septum and for presence of hematocolpos cephalad to the obstruction. Initial imaging usually involves transvaginal ultrasound, though MRI is preferred to identify septum thickness and precise septum location prior to surgical correction [54].

Management

In general, we recommend resection at puberty to allow for improved healing of the vaginal epithelium in the presence of physiologic estrogen levels. Method of surgical repair depends on septal thickness. For thin septa, resection with vaginal epithelial reapproximation is appropriate. When the septum is thick or partial atresia of the vault exists, use a modified Z-plasty technique [71]. This involves creating vaginal epithelial flaps with subsequent proximal to distal flap approximation to add up to

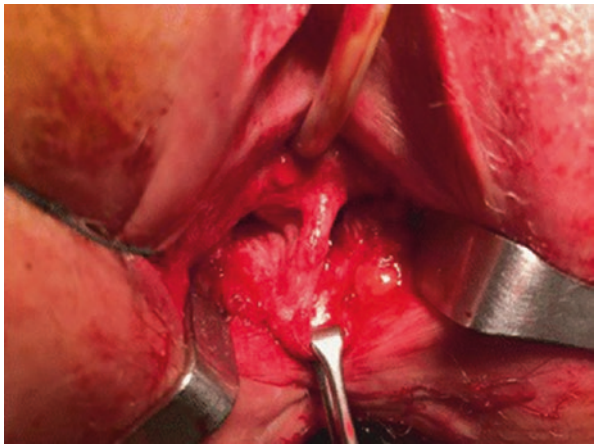

Fig. 11.8 Longitudinal vaginal septum. (Presented with permission from Gallo et al. Martius' flap for recurrent perineal and rectovaginal fistulae in a patient with Crohn's disease, endometriosis and a Mullerian anomaly. In BMC Surg; 2017)

1 cm of vaginal vault length. To minimize the risk of stenosis, patients use a plastic vaginal stent and topical estrogen during the postoperative period [72].

Longitudinal Vaginal Septum

Description and Etiology

Longitudinal vaginal septa are rare, congenital vertical partitions within the vagina that may extend partway or through the full vaginal length (Fig. 11.8) [73]. Septa result from incomplete lateral fusion and/ or resorption of caudal Müllerian ducts.

Presentation

Presentation varies based on septa location and length. Septa are frequently asymptomatic and detected incidentally during routine examination or delivery. If obstruction of one segment occurs (a hemivagina), adolescents will have normal menarche and early cycles but will present later with cyclic unilateral vaginal and pelvic pain due to build-up of menstrual products above the obstructing septum [74]. Symptoms may also include intermittent purulent discharge due to infection of the obstructed hemivagina. It is generally diagnosed several years after menarche as these patients exhibit regular menstruation from the unobstructed vaginal canal [75]. Alternatively, longitudinal septa may present with dyspareunia or tampon failing to obstruct menstrual flow due to placement in only one of the replicated vaginas.

Associations

As with other reproductive tract anomalies, patients with longitudinal septa commonly have associated urinary system anomalies (20–30% of cases). In cases of obstructed hemivagina, there is almost always associated ipsilateral renal agenesis. Concomitant anorectal malformations have also been reported [54].

Longitudinal septa are also associated with uterine didelphys, with approximately 75% of patients with uterine didelphys also having a hemivagina [76, 77]. Herlyn–Werner–Wunderlich syndrome (HWWS) is a rare condition that features the triad of uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis. The syndrome is also referred to as "obstructed hemivagina and ipsilateral renal agenesis" (OHVIRA) and has an estimated occurrence of 0.1–3.8% [30]. This triad is best understood embryologically, as the ureteral bud sprouts from the opening in the urogenital sinus of the Wolffian duct, the absence of one of these ducts may cause renal agenesis, a blind or atretic ipsilateral hemivagina, and a uterine anomaly [78].

Diagnosis

Vulvar exam is normal in these patients. On digital exam, a lateral bulge may be felt at the top of an unobstructed hemivagina. This bulge may also be felt on rectal or abdominal exam in chronic obstruction. Perform a careful pelvic exam to evaluate septum length and to confirm the presence and number of cervices. Initial imaging is done with pelvic ultrasonography followed by confirmatory MRI. Transvaginal ultrasound is rarely tolerated in these patients. Evaluate for other uterine and renal anomalies with appropriate imaging as outlined above.

Management

Asymptomatic patients are managed conservatively, but if symptoms arise the septum should be excised. The most common technique involves serial resection and suture ligation of each segment. Alternatively, the entire length of the septum can also be clamped and then transected with a monopolar blade or needle electrode before closing the incisions. Recently, LigaSure™ (Medtronic/Covidien Minneapolis, MN) and ultrasonic shears have been used for septum transection, due to the small jaw to maneuver tight vaginal spaces, and minimal thermal energy spread, to reduce likelihood of bladder or rectal injury.

Postoperative stenosis or adhesion formation is rare, but reassessment in 2–4 weeks is recommended to break down anteroposterior adhesions that may have formed. If stenosis is a concern, a vaginal mold may be considered postoperatively to minimize vaginal stricture and scarring.

Obstruction and Endometriosis

Endometriosis is more frequent in women with outflow obstruction, hematometra, or hematocolpos, and patients with complete obstruction have higher rates of endometriosis than those with partial obstruction [23–25, 30]. Likewise, those with complete obstruction also experience earlier disease onset with more serious complications. Overall, endometriosis is diagnosed in approximately 40% of cases of obstructed reproductive anomalies [30].

As discussed above, HWWS involves hemivaginal obstruction and is commonly associated with endometriosis. Nearly 20% of women with HWWS will develop endometriomas, compared to 6–10% in the general population. Ovarian endometriotic implants tend to be ipsilateral to the vaginal septum [30]. Early and accurate preoperative diagnosis is key in patients with HWWS.

As less than 10% of adolescents with endometriosis present classically with dysmenorrhea, clinicians need a high index of suspicion for endometriosis in patients with Müllerian anomalies [79]. Likewise, adolescents with suspected endometriosis should be evaluated for obstructive reproductive tract anomalies [80]. Although early diagnosis of endometriosis can prevent distortion of normal anatomy and reduce loss of fertility, delayed diagnosis is common, and most patients are not diagnosed until about 1 year after onset of pelvic pain [30]. In patients with complete obstruction and pelvic pain, concurrent laparoscopy is recommended to assess and treat retrograde menstruation-related sequelae.

Clinicians must be aware that patients with anomalies may develop extensive endometriosis, especially those with obstructed outflow tracts [21]. Initial management involves relief of outflow obstruction and removal of visible endometriotic lesions. Endometriosis, even at advanced stages, may resolve after correction of outflow obstruction [21]. However, disease persists in some patients, perhaps due to peritoneal seeding with prior implants that remain active [81, 82]. Retrograde menstruation may also persist in these patients, or endometriosis may occur by alternative mechanisms such as coelomic metaplasia or immunologic deficiencies.

For many adolescents with reproductive tract anomalies and endometriosis, pelvic pain or discomfort will be a lifelong experience despite medical intervention. Thus, ideal treatment of adolescents with chronic pelvic pain involves a multidisciplinary approach that combines surgical and medical management with pain education, physiotherapy, and psychological therapies. Such interventions have been shown to improve severity of pain and functional quality of life and to reduce health care utilization [83].

Conclusions

Endometriosis is common among adolescents with reproductive tract anomalies, particularly those with obstructive malformations. Although the cause of endometriosis is not definitely known, current research suggests the retrograde

menstruation likely contributes to its pathology in patients with such anomalies. All patients with reproductive tract anomalies and pelvic pain should be evaluated for endometriosis and treated with medical therapy along with surgical excision of active endometrial remnants. Greater research is needed to fully elucidate the cause of endometriosis in these patients and more effectively treat both their pathology and symptoms.

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Chapter 12
Obstructed Mullerian Anomalies and Endometriosis in the Adolescent

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Background

It is well established that obstructive uterine anomalies confer a higher risk of endometriosis; this is congruent with the theory of retrograde menstruation as an etiology of endometriosis and is further supported by the distribution of endometriosis noted in the group of patients with obstructive Mullerian anomalies, which often corresponds to the laterality of obstruction. The outflow obstruction caused by functional occlusion of the endocervical canal and concurrent retrograde neonatal uterine bleeding may even explain premenarchal endometriosis [9]. While this dissemination of neonatal endometrial stem cells cannot be addressed as readily, the ongoing outflow obstruction caused by anatomic uterine anomalies certainly increases the severity of subsequent disease. Thus, the earlier diagnosis and correction of obstructive uterine anomalies may allow for prevention of progression of endometriosis. This becomes especially difficult in cases of hemiobstruction or incomplete obstruction, as the presence of normal menses may lead the clinician away from the correct diagnosis or pelvic pain. Case studies have shown complete resolution of endometriosis in those with an obstructive anomaly after surgical correction [37]. However, data on the resolution of endometriosis in those with obstructive anomalies are mixed, and some do not experience resolution of pain symptoms, underscoring the importance of early diagnosis and management. An important key

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to early diagnosis and proper management is classification of the anomaly. Various classification systems have been proposed. Initially, classification systems were based largely on embryologic development [4], including Acien's classification system based on embryologic origin and related clinical symptoms [1, 3]. In recent years, the European Society for Human Reproduction and Embryology (ESHRE)/ESGE classification system as well as the American Society for Reproductive Medicine (ASRM) classification system have been developed, with the ESHRE/ESGE system based on anatomical considerations, separating malformations of the corpus uteri, cervix, and vagina [30, 20]. The ASRM system, which is the most widely used, is a descriptive system in which malformations are separated by class via a scoring system into seven basic groups [30, 39].

Diagnosis of Uterine Anomalies

Mullerian anomalies are rare, and the diagnosis of an obstructed Mullerian anomaly in an adolescent is often delayed, as these anomalies are not considered in the initial differential diagnosis. The diagnosis of Mullerian anomalies is dependent upon the type and location of the anomaly. Anomalies of the external genitalia can often be visualized at birth. On the other hand, internal anomalies, specifically those with an obstructive component, are more frequently diagnosed around the time of menarche. Those without an obstructive component are usually diagnosed during adolescence or at the onset of sexual activity. In patients with an obstructive anomaly, the accumulation of menstrual blood can lead to hematometra, hematosalpinx, and hematocolpos; over-distention of the uterus, fallopian tubes, and vagina, respectively. Gastrointestinal and genitourinary symptoms such as urinary frequency or retention, constipation, nausea vomiting, and diarrhea can also be present due to mass effect and mechanical obstruction [15]. A large pelvic mass may also lead to ureteral compression and hydronephrosis.

Obstructive anomalies can be divided into those with a complete outflow obstruction and those with a unilateral or partial outflow obstruction. Complete outflow obstruction anomalies will present at menarchal-age with delayed menarche, primary amenorrhea, acute, cyclic/intermittent, or chronic pelvic and/or abdominal pain. As menarche generally occurs 2 years following the start of breast development (thelarche), intermittent or cyclic pelvic/abdominal pain in a female who is 2 or more years from thelarche should raise concern for an obstructed Mullerian anomaly. The onset of these pain symptoms will vary with the level of obstruction: an imperforate hymen will typically present later than a high transverse vaginal obstruction or cervical agenesis, as the vaginal distention with the accumulated menstrual blood can be relatively asymptomatic at first, whereas uterine distention and retrograde menstruation occur sooner after menarche with a high level of obstruction and onset of pain occurs soon after menarche and is more severe. A unilateral obstruction is more challenging to

diagnose as menarche occurs in a typical fashion and symptoms are often attributed to "normal" dysmenorrhea. However, with a unilateral obstruction, the symptoms are different and can be elicited with a careful history. A unilateral complete obstruction will typically cause pain that is worse on the side of the obstruction compared to the non-obstructed side. Therefore, it is important history to elicit the location of the dysmenorrhea/pain, if it is worse on one side, if the severity is increasing with each menstruation. Eventually, the pain may be chronic with exacerbations linked to menstruation.

A partial obstruction or microperforation may be present in an obstructed anomaly or unilateral obstructed anomaly. This anomaly is typically associated with some degree of hematocolpos/hematometra, but has unique presentation of prolonged menstruation or intermenstrual spotting, as it takes longer for the partially obstructed side to drain accumulated blood. The partially obstructed side can also become infected leading to pyocolpos/pyometra with purulent, malodorous vaginal discharge, and, rarely, progression to sepsis [7, 13].

Unfortunately, many of these symptoms can be overlooked by medical providers due to the baseline prevalence of primary amenorrhea, dysmenorrhea, and pelvic pain in the early adolescent population. These are frequent complaints among young women around the time of menarche, and therefore a delay in diagnosis of an obstructive anomaly is unfortunately common [7]. Expectant management is often the first course of action, followed by temporizing medical therapy using nonsteroidal anti-inflammatory drugs (NSAIDs), as well as oral contraceptive pills. Administering these to the patient can delay the diagnosis even further due to partial symptomatic relief.

Physical exam is also an important part of the evaluation. In these adolescent patients, this exam includes tanner staging, and a preliminary examination of the external genitalia including the hymenal orifice and an abdominal exam to assess for tenderness and masses. [7]. In the case of an imperforate hymen, or other obstruction low in the genital tract such as a distal vaginal transverse septum or agenesis, applying abdominal or suprapubic pressure manually or with Valsalva can also reveal a bulge at the introitus due to accumulated menstrual blood in the vagina (hematocolpos/hematometrocolpos). In patients who have a unilateral obstructed anomaly, menstrual bleeding will occur from the non-obstructed side, while the obstructive symptoms described above are present on the obstructed side. However, an internal pelvic exam in these young females may be difficult and can be deferred to obtain imaging. In certain circumstances, an exam under anesthesia may be warranted.

In addition to a physical exam, laboratory studies can be performed. These aid in diagnosis by helping to differentiate Mullerian anomalies from other disorders including those of sexual differentiation. These tests include measuring gonadotropins and sex steroid hormone levels, as well as performing a karyotype [28]. As Mullerian anomalies affect only the uterus and vagina and are typically associated with normal ovaries, these hormone levels and karyotype will be consistent with normal female ranges.

Imaging studies helpful in the diagnosis of these disorders include ultrasonography (US), three-dimensional ultrasonography (3D-US), magnetic resonance imaging (MRI), and hysterosalpingogram (HSG). A pelvic ultrasound is the preferred initial imaging modality. Depending on the age and tolerance by the patient, different modalities of ultrasound can be used to visualize the pelvic organs. In prepubertal or adolescent patients, transabdominal ultrasound is usually the first imaging modality used. It is performed with a distended bladder in order to provide an acoustic window. Sonocolpography is a procedure during which a catheter with a balloon is placed inside the vagina, and abdominal ultrasound is performed simultaneously. It is used to better assess the relationship of the vagina to the remainder of visualized pelvic organs, which is helpful with anomalies such as a transverse vaginal septum [43]. Transvaginal ultrasonography is traumatic for a young female, but may be appropriate for sexually active adolescents and adults, as it renders improved tissue delineation compared to abdominal imaging. Transperineal ultrasound can be helpful in supplementing abdominal or vaginal imaging, especially in providing information such as the distance between the perineum/introitus and the obstructed portion of the vagina [40]. Transrectal ultrasonography can also be of diagnostic assistance, specifically in the assessment of congenital vaginal canalization anomalies. Three-dimensional ultrasonography is comparable to MRI for congenital uterine anomalies but may not be ideal for complex uterine, cervical, or vaginal anomalies [8].

MRI is the imaging gold standard for diagnosis. Although ultrasound on its own can sometimes be sufficient for diagnosis, an MRI is often necessary for combined vertical and lateral anatomic defects [34]. An MRI will provide clear demarcation of the uterine, cervical, and vaginal anatomy simultaneously and is less operator dependent. It can be used to more clearly assess the length of the vagina, measure the thickness of a utero/vaginal septum when present, and to delineate both the number and configuration of cervix/cervices and uteri when necessary. In the cases of a duplicated Mullerian system, an MRI is especially useful in distinguishing the presence of communication between the pelvic structures, as well as determining whether or not functional endometrium is present in uterine horns. MRI obtains simultaneous images in multiple planes, with a larger field of view than ultrasonography. While ultrasonography utilizes sound waves, MRI uses magnetic fields in which hydrogen molecules are excited, and their relaxation back to baseline is subsequently evaluated; images are produced based upon this information. Both longitudinal (T1) and transverse (T2) relaxation time can be measured. Transverse relaxation is especially helpful in delineating the zonal anatomy of the uterus and vagina and identifying Mullerian structures. The signal differentiation in these studies is also useful in distinguishing endometrial tissue from the myometrium, and vaginal mucosa from the submucosa and adventitia [7].

HSG can be used to assess endometrial shape, tubal patency, and communication between uteri, cervices, and vaginas in the case of a duplicated system. HSG is performed by introducing radiopaque water-soluble contrast into the endometrial canal. However, in order to perform this exam, patients must first tolerate a speculum exam and have a patent vaginal and cervical canal. This test is therefore, in general, of limited diagnostic use in adolescents, unless performed under

anesthesia. In terms of obstructive anomalies, it is most useful in evaluating the patency between duplicated Mullerian structures in complicated anomalies, or determining the presence of a microperforation when one is suspected [1].

Renal and ureteral imaging is often performed in patients with congenital reproductive tract anomalies, as they have a high incidence of accompanying urinary tract anomalies. This association is attributed to the simultaneous embryologic development of the paramesonephros and metanephros. Ultimately, 30–50% of Mullerian anomalies will have an associated nephron-ureteral anomaly. Examples of such anomalies include unilateral renal agenesis, duplex collecting systems, horseshoe kidneys, and ectopic/pelvic kidneys. Renal and ureteral anatomy can be assessed by X-ray, ultrasonography, and MRI [7]. An intravenous pyelogram (IVP) can also be used to further visualize abnormalities of the urinary system. It uses timed intravenous contrast, which is excreted through the kidneys, and serial X-rays to highlight the entirety of the urinary tract.

When making an accurate diagnosis of one of these conditions, surgical intervention is sometimes necessary. This can include an exam under anesthesia (EUA), vaginoscopy (one can use a cystoscope or hysteroscope to perform this procedure), hysteroscopy, and diagnostic laparoscopy. EUA and vaginoscopy are useful to clarify the length of the vaginal canal and to assess vaginal and cervical malformations. Performing a concurrent laparoscopy and hysteroscopy (when there is a patent vaginal and cervical canal) can be used to diagnose such anomalies, in order to assess inner and outer contour of the pelvic organs simultaneously. Complex anomalies may necessitate a diagnostic laparoscopy, in order to clarify anatomy and resolve uncertainties from imaging studies.

Obstructive Anomalies

Obstructed Hemivagina and Ipsilateral Renal Anomaly (OHVIRA)

Of obstructive anomalies, the most common is double uterus with obstructed hemivagina, otherwise known as obstructed hemivagina ipsilateral renal anomaly syndrome (OHVIRA) [38] also known as Herlyn–Werner–Wunderlich syndrome (HWW) [25]. This most classic variant of OHVIRA with a didelphic uterus, obstructed hemivagina, and ipsilateral renal agenesis accounts for about 72% of cases [17]. The obstruction is characterized by a unilateral vaginal septum leading to obstruction of the outflow tract in the right or left hemivagina and can often be noted on imaging with unilateral hematocolpos. In the majority of cases, the obstructed hemivagina and ipsilateral renal agenesis is present on the right side [24, 44]. Other findings in nonclassic variants included permutations of the classic form with finding such as complete septate uterus, bicornuate bicollis uterus, monolateral cervical atresia, and septate cervix with obstructed hemivagina [17] (Figs. 12.1, 12.2, and 12.3).

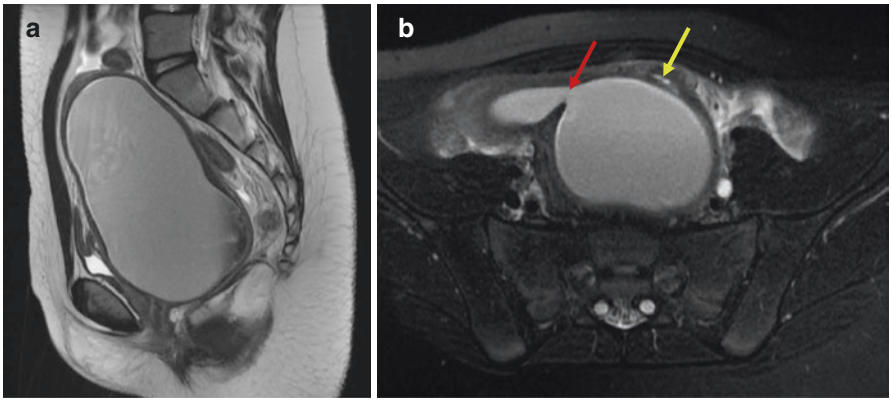

Fig. 12.1 Uterus didelphys, with obstructed hemivagina. (Figure with permission from Samantha Pfeifer MD)

A. Sagittal view demonstrating the size of the Right hematocolpos in the obstructed right hemivagina

B. Transverse view showing the cross-section of the distended right obstructed hemivagina, the right cervix, and right hematocolpos. Note the right cervix is well defined (red arrow). The compressed normal left hemivagina is seen (yellow arrow)

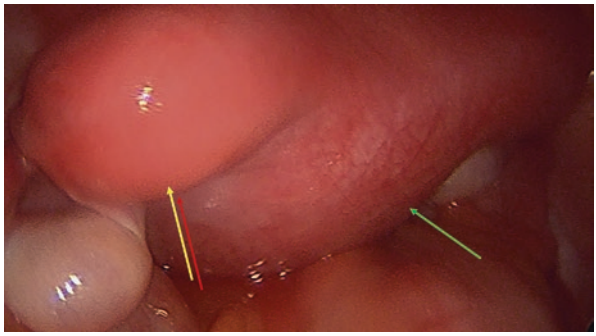

Fig. 12.2 Uterus didelphys, obstructed right hemivagina: the normal left hemiuterus (yellow arrow) is seen above the distended right hemivagina (green arrow). (Figure with permission from Samantha Pfeifer MD)

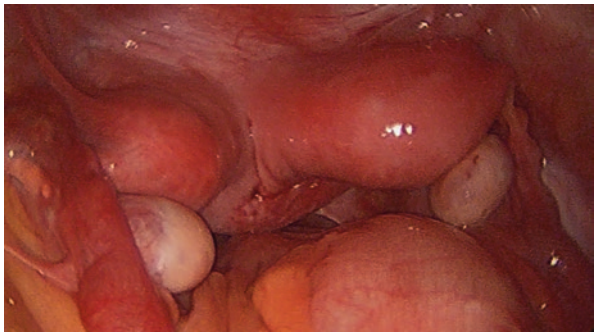

Fig. 12.3 Uterus didelphys, obstructed right hemivagina: following decompression. Didelphic uterus seen more clearly now that hematocolpos is decompressed. (Figure with permission from Samantha Pfeifer MD)

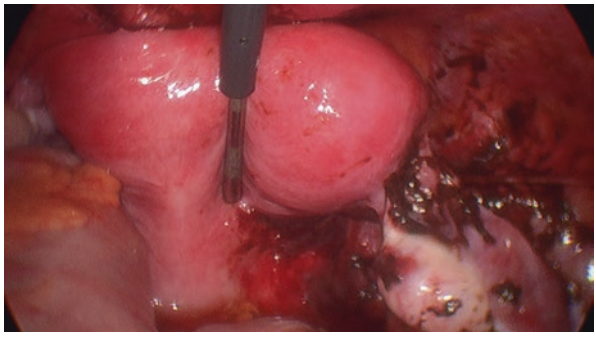

Fig. 12.4 Complete septate uterus with obstructed right hemivagina. Note development of endometriosis on the right side from retrograde menstruation caused by the obstruction. (Figure with permission from Samantha Pfeifer MD)

Presentation

Patients with OHVIRA may present with a variety of symptoms including dysmenorrhea usually worse on one side, vaginal discharge, unilateral abdominal pain, chronic pelvic pain, and urinary incontinence. In the case of a microperforation in the obstructed side, presentation is typically prolonged intra-menstrual spotting or purulent vaginal discharge, rarely sepsis may occur. These individuals are typically found to have a paravaginal mass, pyocolpos, or hematometra on further exam and workup [10]. The age at presentation is dependent on whether hemi-obstruction is complete or incomplete with those having a complete obstruction presenting closer to menarche, with a mean age of 13 versus 24.7 for those with an incomplete outflow obstruction [24]. Delay in diagnosis is associated with development of endometriosis seen primarily on the side of the obstruction, which can lead to tubal damage, adhesive disease, ovarian endometrioma formation, infertility, and pain (Fig. 12.4).

Management

The corrective approach depends on the mechanism of obstruction. In the case of the classic form of OHVIRA, surgical excision of the vaginal septum and marsupialization of the blind hemivagina correct the outflow obstruction. Laparoscopy is not necessary, but may be considered at the time of vaginal septum resection for indications of pelvic mass, suspected endometriosis, abscess, or infertility [24]. Hysteroscopic resection of the vaginal septum can be utilized in a virginal patient to preserve the hymen [31]. In the case of a small upper vaginal collection or significant distance from the patent outflow tract, a hemihysterectomy with resection of the associated hemivagina may be performed. If uterine horn sizes are found to be equivalent, a metroplasty may be considered but should only be undertaken with an experienced surgeon [32]. In the case of cervical atresia, a laparoscopically assisted cervicoplasty allows for correction [17]. When postponement of surgery is required, treatment with GnRH agonists with addback therapy with norethindrone acetate should be employed to maintain amenorrhea [24]. Laparoscopic drainage of the

hematocolpos is not recommended as primary surgical intervention since the hematocolpos will recur and as the size of the hematocolpos is reduced, marsupialization of the obstructed side is more difficult. Transvaginal drainage of the hematocolpos places the patient at risk of subsequent infection and should be avoided.

Unicornuate Uterus with Obstructed Uterine Horn

The normal maturation of the Mullerian duct with the absence or partial development of the contralateral duct gives rise to a unicornuate uterine configuration. Outflow obstruction can occur when the contralateral duct develops partially, giving rise to a rudimentary horn, which can be either communicating or noncommunicating and cavitating or noncavitating. Approximately 74–90% of unicornuate uteri are associated with a rudimentary horn [41], and 20–25% of women with a unicornuate uterus have a rudimentary horn that is both cavitating (or functional) and noncommunicating [18]. Patients may also have ipsilateral renal agenesis. In a case series, two out of three patients with a rudimentary horn that was cavitating and noncommunicating had ipsilateral renal agenesis [25].

Presentation

An obstructed uterine horn whether or not associated with a rudimentary horn will commonly present with primary amenorrhea and cyclic pelvic pain. The pelvic pain presenting after menarche may be progressive, caused by worsening hematometra, hematosalpinx, or endometriosis (Fig. 12.5). Patients may also present with an endometrioma ipsilateral to the noncommunicating horn [1] (Fig. 12.6). In one study, about 55% of patients with a noncommunicating horn presented with pain [23]. However, even in those with a cavitating and noncommunicating horn,

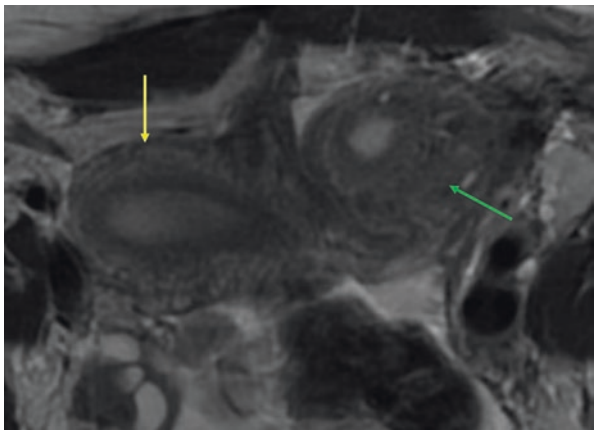

Fig. 12.5 MRI of right hemiuterus normal (red arrow) and blind left uterine horn (yellow arrow) with functional endometrium within. (Figure with permission from Samantha Pfeifer MD)

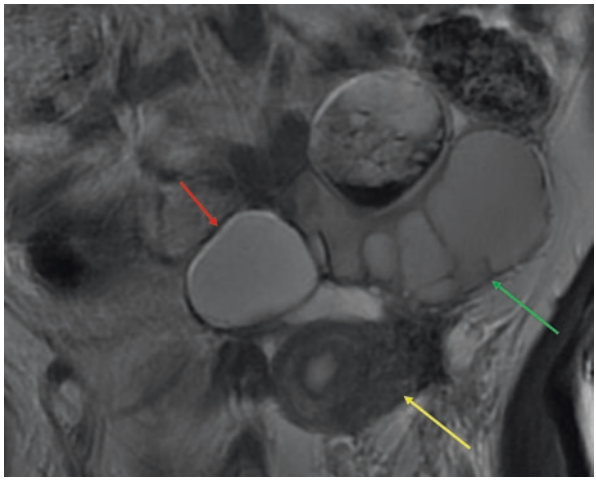

Fig. 12.6 Left blind uterine horn (yellow arrow) with large left hematosalpinx (red arrow) and left ovarian endometrioma (green arrow) as a result of delayed diagnosis and continued retrograde menstruation. (Figure with permission from Samantha Pfeifer MD)

hypoplasia of the endometrium and abnormal development of the endomyometrial junction could contribute to a less than normal menstruation and mitigate hematometra, development of endometriosis, and pain symptoms. In the case of a communicating rudimentary horn or noncavitating horn, pain may not be associated with the presentation [13], and given a lack of outflow obstruction, endometriosis should be less likely to develop. However, all configurations can still result in pelvic pain or other symptoms. Commonly, patients in all subgroups will be asymptomatic, and unfortunately, diagnosis is usually delayed, with 78% of patients presenting in the third decade of life or later [23].

Management

The extent of endometrial activity within a rudimentary horn as well as its extent of connection will influence management [23], as much as it may influence symptomatology. Surgical approach is generally laparoscopic with removal of a rudimentary uterine horn. However, an open approach may also be considered, based on other individualized anatomic or historical factors, as well as surgeon familiarity. Hysteroscopy or hysterosalpingography may be useful to elucidate whether a small communication exists, by determining the presence of one or two tubal ostia. In this case, oversewing of this area of communication is important to prevent weakness at the uterine wall in this location [13]. Hysteroscopy may also have utility in providing transillumination for laparoscopic dissection when a broad connection is present [18] and will help reduce the risk of damage to the contralateral horn [23]. Treatment with a GnRH agonist can be considered preoperatively to reduce the size of hematometra; however, distention with menstrual blood may actually be a factor that helps delineate the rudimentary horn [18]. Noncavitating uterine horns may be left in situ [23], especially if asymptomatic. However, noncommunicating horns and the

ipsilateral fallopian tube place the patient at risk for pregnancy in either the uterine horn or fallopian tube, which may result in a life-threatening situation [41]. The patient should be counseled regarding these risks, and surgical excision prior to pregnancy may be considered.

Cervical Agenesis and Uterine Isthmus Agenesis

Cervical agenesis, or the complete failure of cervical development, is a rare Mullerian anomaly that nonetheless has significant consequences on a woman's life and reproductive capacity. This condition has several manifestations, the most severe being the complete failure of development of cervical tissue. Other variations include the presence of different degrees of cervical tissue [36]. Other anomalies described display normal cervical development with distal occlusion of the cervical canal. Some patients may have otherwise normal cervical development with complete absence of the uterine isthmus (agenesis) and cervical canal. Others may only have a fibrous band of tissue in lieu of a cervix, with few intermittent areas of endocervical tissue [36, 29]. Fifty percent of cases of cervical agenesis are associated with vaginal agenesis or atresia. Some may also be associated with uterine anomalies such as unicornuate, bicornuate, or didelphys uteri. The risk of associated nephro-ureteral anomalies is 10–25% [36, 19].

Presentation

These conditions are usually diagnosed in early adolescence with pelvic pain in the setting of primary amenorrhea. Pain occurs due to over-distention of the uterus and fallopian tubes with menstrual blood (hematometra and hematosalpinx, respectively), as well as peritoneal irritation from significant retrograde menstruation via efflux of blood from the fallopian tubes into the peritoneal cavity [16]. Patients with cervical agenesis usually present soon after the first menstrual bleed with pain, unlike obstructive anomalies of the distal vagina or hymen, which may present months after the first menstrual bleed as the vagina is distensible and can accommodate a significant amount of accumulated menstrual blood. In addition, patients with cervical agenesis rarely present with a large palpable abdominal-pelvic mass, as the uterus itself is not very distensible. If a mass is palpable, it is more likely to be due to hematosalpinx or an ovarian endometrioma [33].

Management

Although ultrasonography is helpful as an initial imaging modality in these patients, ultimately MRI will likely be necessary. MRI can effectively differentiate cervical agenesis from other obstructive conditions, in particular high transverse vaginal

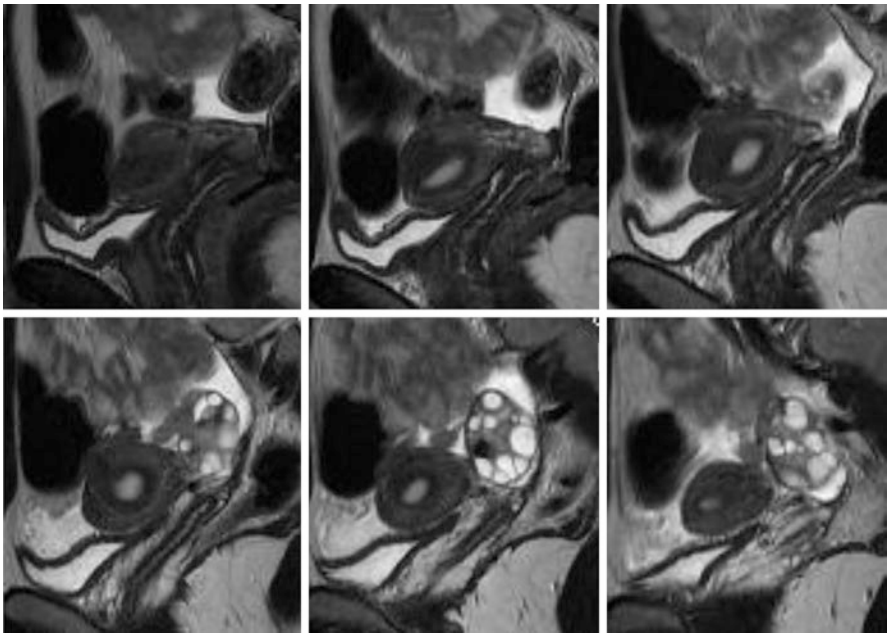

Fig. 12.7 MRI T2-weighted sagittal view series across pelvis showing of uterus demonstrating absence of cervix. (Figure with permission from Samantha Pfeifer MD)

septum, and can assess the extent of agenesis and composition of any cervical tissue present (Figs. 12.7 and 12.8).

Treatment of cervical agenesis and uterine isthmus agenesis will require surgical intervention. However, surgery may be deferred by suppressing menstruation to allow access to an appropriately experienced surgeon or to allow the patient to mature, so she may be involved in the decision-making process. These medical therapies include continuous oral contraceptive pills, continuous progestins (norethindrone acetate or depot medroxyprogesterone acetate), or GnRH agonist therapy with add-back hormonal supplementation [29]. If the uterus still needs to be drained of hematometra as a temporizing measure, this should be done laparoscopically rather than vaginally in order to reduce the risk of ascending infection [19].

Traditional treatment of these disorders used to be mostly limited to hysterectomy. Attempts had previously been made to create a fistulous tract from the vagina to uterus to treat complete cervical agenesis. However, this resulted in a high incidence of reoperation due to reocclusion of the fistulous tract with the need for subsequent hysterectomy, as well as reoperation due to sepsis [19, 36, 14].

However, several newer studies evaluating uterovaginal anastomosis, rather than fistulous tract surgery, have showed higher success and lower complication rates. The sample sizes of these studies are small, between 12 and 18 patients per study. Yet two studies had no complications [11, 16], one study had one incident of restenosis and infection requiring hysterectomy [26], and one study had two incidents of

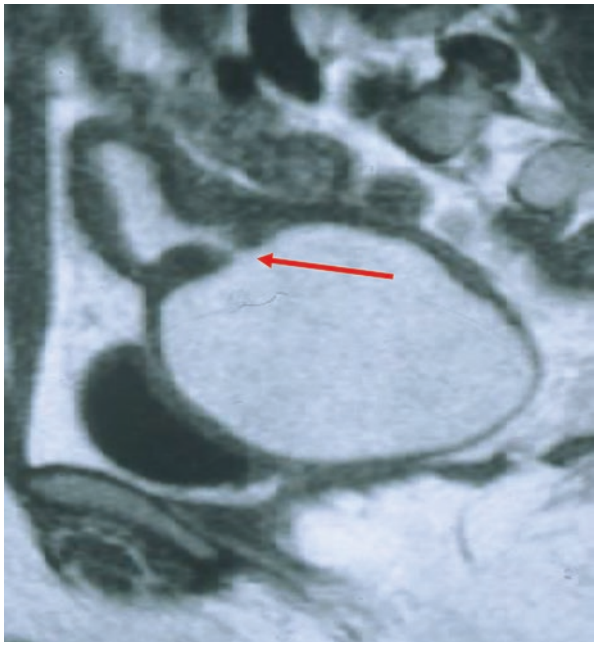

Fig. 12.8 MRI sagittal view showing high transverse vaginal septum with clearly demarcated cervix (yellow arrow) above hematocolpos. (Figure with permission from Samantha Pfeifer MD)

recurrent stenosis, one of which resulted in infection [12]. Of these newer studies, those which have had patients attempt pregnancy after surgery have all had successful pregnancies and subsequent viable deliveries; in this group, there has been only one pregnancy loss to date.

In patients undergoing a uterine-vaginal anastomosis, the surgery is performed concomitantly from a vaginal and abdominal approach. The procedure is initiated vaginally, with attempts to identify any cervical tissue present. The uterus is mobilized from above by laparoscopy or laparotomy. An opening is then made from above through the uterine fundus, and a probe is placed through this opening to the level of the cervical tissue or utero-vaginal junction. This facilitates the location of the junction from a concomitant vaginal approach, after which dissection is performed from below to locate the uterus. This dissection starts at the apex of the vagina, longitudinally along the rectovaginal and vesicovaginal planes. The inferior opening into the uterus or hypoplastic cervical area can be made via a single incision or in a cone-like fashion. Once a complete communication is achieved, the open cervico-uterine area is anastamosed to the upper vaginal edges. This is done from above or vaginally using interrupted delayed absorbable sutures. A silicone stent is placed from the vagina through the aperture and into the uterus in order to maintain cervical patency [36, 19, 16, 26]. This can be sutured in place using delayed absorbable sutures such that the stent will fall out once the sutures are absorbed; if only a few sutures are placed from below, these could also be removed manually in the future. The stent can also be left in place without sutures if the utero-vaginal sutures themselves are tied tightly down around the stent in order to compress it. The stent will either eventually fall out on its own or can be removed manually.

In patients with associated vaginal agenesis in addition to cervical agenesis, surgical options for the concomitant vaginal correction include a modified McIndoe approach. These patients ideally first undergo treatment with serial vaginal dilation for 6–9 months if possible, in order to achieve adequate vaginal length prior to their surgical procedure. This may preclude the need for grafted tissue to help create a neovagina. In the McIndoe approach, graft tissue is used to line the neovaginal space that is connected to the newly created cervical aperture. The tissue for this graft can be from a split thickness skin graft, amnion, buccal mucosa, or autologous in vitro cultured vaginal tissue. Until these patients are able to be sexually active, a vaginal mold is worn postoperatively in order to prevent contraction of the graft. Successful vaginal patency is seen in up to 68% of these patients [21, 46, 42].

Pregnancies have been reported in women following uterovaginal anastomosis both spontaneously and after IVF [12, 19, 11, 5]. Of those reported in the literature age at delivery ranged from 31 to 38 weeks. Cervical cerclage was not described in any of the patients. Uterine isthmus agenesis is a very rare condition with only two cases reported [35, 45], and there is no information regarding pregnancy. In patients who have restenosis of the cervix after surgical intervention, a pregnancy via in vitro fertilization (IVF) with ultrasound-guided transmyometrial embryo transfer is possible [6, 27, 22].

Complex Mullerian Anomalies

Complex Mullerian anomalies, otherwise known as Mullerian anomalies "without a classification" include those that deviate from the previously documented categories of said anomalies or combine elements of more than one category [2]. These atypical cases are rare and isolated, with varying degrees of abnormal fusion and reabsorption, affecting differing portions of Mullerian duct development. These anomalies are difficult to describe using current classification systems. Many of the atypical anomalies involve two uterine remnants with or without cervical tissue and with communication between the remnants at the level of the cervix, vagina, or uterine body [2, 1]. Sorting out the actual anatomy can be challenging and may require MRI, exam under anesthesia, laparoscopy, hysteroscopy, vaginoscopy, as well as hysterosalpingography. The degree of obstruction and subsequent retrograde menstruation differs in these anomalies depending upon the specific anatomic variations, and whether they contain mostly fusion defects of the superior uterine segment or resorption defects of the inferior uterine segment and vagina. As these anomalies are not otherwise classified, understanding the marked ways in which these conditions differ in embryological origin helps to elucidate the mechanisms by which obstruction, and subsequent symptoms and sequelae can occur. It is also beneficial in planning surgical treatment modalities when warranted.

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Chapter 13
Adenomyosis in Adolescence

Ourania Koukoura and George Pistofidis

Introduction

John Sampson noted in his 1921 article that adenomyosis (i.e., endometriosis) and certain hemorrhagic cysts were in fact the same disorder, only manifesting in different areas [1]. Adenomyosis is a benign disease characterized by the presence of ectopic endometrial tissue within the uterine myometrium, resulting in pockets of endometrial glands surrounded by hypertrophic smooth muscle [2]. Diffuse adenomyosis is the most common form, while nodular and cystic forms are rare [3]. While adenomyosis is commonly reported in women over 30 or perimenopausal and multiparous women, there is growing evidence of adenomyosis affecting young women [4]. Although the available literature is mainly consisted of case reports and case series, adolescents represent a subset of patients where the diagnosis of cystic adenomyosis is more frequently established, especially when severe dysmenorrhea and chronic pelvic pain are present.

Epidemiology

Adenomyosis has been defined as a disease of adult life. A century ago, Meyer examined 100 uteri from fetuses, newborn girls, and children and concluded that mucosal invasion of the myometrial layer was seldom detected [5]. Although later studies identified histologic features of adenomyosis in young women, until recently, no reference has been made of the disease during adolescence [6–8]. The actual

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incidence of adenomyosis in adolescence is basically unknown, since the current literature is based on small case series and case reports [9–12]. Another major limitation on the estimation of the prevalence of juvenile adenomyosis is the lack of accurate definition and diagnostic criteria. Cystic adenomyosis has been described as a noncommunicating accessory uterine cavity, suggesting a type of congenital uterine anomaly. Adenomyosis in adolescence therefore has been previously described as juvenile cystic adenomyosis, as juvenile adenomyotic cyst, or as an accessory and cavitated uterine mass [13]. Recent advances in imaging techniques and improved awareness of the disease led to the emergence of several articles investigating the pathophysiology and implications on diagnosis of adenomyosis in younger patients. Most studies however emphasize on the need of a high degree of suspicion in every case of a young girl with severe dysmenorrhea or pelvic pain refractory to common analgesics [14].

Pathophysiology

The variant of adenomyosis that is specific to adolescent women is the so-called cystic adenomyosis [8] which represent cystic formations within the myometrium with hemorrhagic content resembling that of an endometriotic cyst. Histologically, these cysts are lined with an endometrial-like layer and surrounded by hyperplastic, hypertrophic smooth muscle layer, macrophage infiltration, and hemosiderin pigmentation [15]. Although the majority of adolescent girls with adenomyosis present with the cystic type of the disease, sporadic reports also describe the diffuse form of adenomyosis in this group of patients [11, 16].

The pathophysiology of adenomyosis is presumed to be due to benign endomyometrial invagination or estrogen stimulation of Müllerian rests. Disruptions of the endometrial-myometrial border are thought to allow for a reactive hyperplasia of the endometrial basalis layer and its extension into the myometrium [17, 18]. Some suggest the triggering mechanism leading to the myometrial invasion is due to either spontaneous (physiologic peristaltic process) or iatrogenic traumatization. In cases of adenomyotic lesions in adolescences, iatrogenic implantation usually does not apply. Specific hormonal (estrogen-progesterone receptor) and immune responses may play an important role on disease progression [17–19]. Takeuchi et al., in a study of nine patients with juvenile adenomyosis (young women), reported that the adenomyotic lesions of all patients were positively stained for CD10, estrogen receptors, and progesterone receptors, similar to normal endometrium [9].

Symptoms

Although endometriosis may be the most common cause of secondary dysmenorrhea in younger patients, adenomyosis should be considered as an alternative diagnosis [20]. In fact, histologically proven endometriosis has been established in 62%

of adolescents undergoing laparoscopy for severe dysmenorrhea [21]. In the majority of cases, primary dysmenorrhea or gradually worsening dysmenorrhea which corresponds to intracystic bleeding and progressive increase of the cyst size are the universal symptoms. Reports suggest that other symptoms may develop over time, such as chronic pelvic pain and/or dyspareunia or abnormal uterine bleeding. As a rule, however, the pain has cyclical characteristics, and it is perimenstrual [22]. The pain is usually unresponsive to analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), or combined oral contraceptive pills (COCPs), which in most cases warrants further investigation.

Diagnosis

Traditionally, a diagnosis of adenomyosis is made histopathologically, following routine hysterectomy. The newer uterine-sparing surgical techniques, however, demand a precise preoperative diagnosis. There are a few obstacles that must be overcome in order for an accurate diagnosis, in cases of adenomyosis in adolescence, to be made. First, the number of cases reported in the literature is relatively small (approximately 30 patients), the majority of whom are women in their 20s or 30s. Reports on adenomyosis in adolescent girls are scarce. Second, what is now characterized as juvenile adenomyosis, or cystic adenomyosis, has been described as congenital Müllerian malformations in previous reports, such as a noncommunicating rudimentary horn, with uterine unicornis. Third, in most of these patients, the first imaging modality used to investigate severe dysmenorrhea is the transabdominal ultrasound which in general has a lower accuracy than the transvaginal one in detecting uterine pathologies.

In 1912, Oliver described a case of a 34-year-old woman with “an accessory uterus distended with menstrual fluid” [23]. Almost a century later, in 1996, Tamura et al. first described “a juvenile adenomyotic cyst of the corpus uteri” measuring 15 mm on the anterior uterine wall in a 16 -year-old girl [24]. Since then, sporadic case reports appeared in the literature recognizing this new entity. Acien et al. proposed the term of ACUM (Accessory and Cavitated Uterine Mass) with a functional endometrium, for juvenile adenomyosis and cystic adenomyosis in general [13]. The diagnostic criteria proposed in that study were (i) an isolated accessory cavitated mass; (ii) normal uterus (endometrial cavity), Fallopian tubes, and ovaries; (iii) a surgical case with an excised mass and histopathology report; (iv) an accessory cavity lined by endometrial epithelium with glands and stroma; (v) a chocolate-brown-colored fluid content, and vi) no adenomyosis (if the uterus has been removed). The authors concluded that most cases of juvenile adenomyosis are in fact ACUMs because they share similar clinical and histopathological characteristics. They also suggested that these lesions may arise from duplication and persistence of ductal Müllerian tissue in the proximal to the round ligament area and proposed an association between this anomaly and a “dysfunction” of the development of the gubernaculum. The diagnostic criteria proposed by Acien et al. were based on cases presented in their studies [13, 25]. The main question that arises,

however, is, since adenomyosis and endometriosis often coincide, how accurate is the prerequisite of the presence of an otherwise normal uterus and ovaries as a diagnostic feature, in order to establish diagnosis.

A decade ago, Takeuchi et al. described the diagnostic criteria of juvenile cystic adenomyoma based on age (<30 years), presence of cystic lesion ≥1 cm in diameter with no detectable connection to the endometrial cavity, and surrounding hypertrophic myometrium, associated with dysmenorrhea. They reported nine cases of juvenile adenomyosis based on these criteria (age ≤30 years, cystic lesion ≥10 mm with no communication with the uterine lumen surrounded by hypertrophic myometrium, and severe dysmenorrhea) [9].

When investigating a case of severe dysmenorrhea in a young girl with adenomyosis, a vaginal or rectal bimanual clinical examination will reveal a painful nodule on the right or left uterine horn [16, 26]. Transvaginal or transrectal ultrasound will detect a single cystic mass, with a ground-glass isoechoic content, similar to that of an endometrioma (Fig. 13.1). Rarely the lesion is detected in the anterior uterine wall. As a rule, the remainder of uterus is normal.

Although the proposed sonographic diagnostic criteria are more or less similar in most reports, magnetic resonance imaging has been widely used to establish diagnosis [28]. Several studies have demonstrated higher sensitivity and specificity rates compared with ultrasound in the diagnosis of adenomyosis. Itam et al. diagnosed adenomyosis using MRI in two adolescents aged 16 years [11]. In one case, a low-signal area in the caudal aspect of the uterus was diagnosed as focal adenomyosis. In the other, the diagnosis was based on a poorly defined junctional zone. Diffuse adenomyosis has also been diagnosed in adolescent patients with thickening of the junctional zone and enlarged uterus on MRI. In their study, Itam et al. stated that the cut-off of the thickness of the junctional zone in cases of adenomyosis in young girls should be lower, since junctional zone anatomy is highly dependent on gonadal hormones and thickness increases gradually with age, to its peak at 41–50 years. On the other hand, an MRI that shows an accessory endometrial cavitation in the myometrium is highly diagnostic [29, 30]. The adenomyotic lesions are detected on MRI as high-intensity areas on T1-weighted images and as hypo- or high-intensity areas on T2-weighted images with negative fat suppression. These features

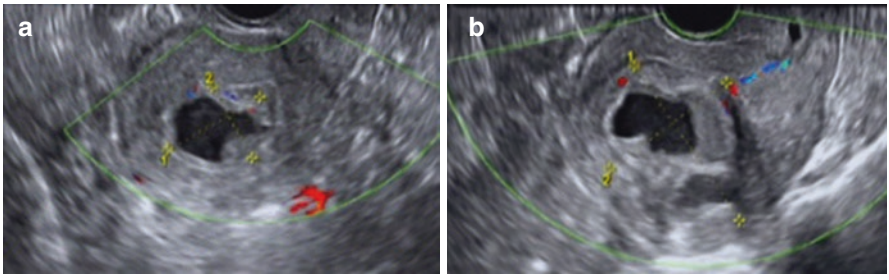

Fig. 13.1 Sonographic images of intrauterine cystic adenomyosis. Regularly shaped lesions with a high-level echo and strong echo halo around the lesions [27]

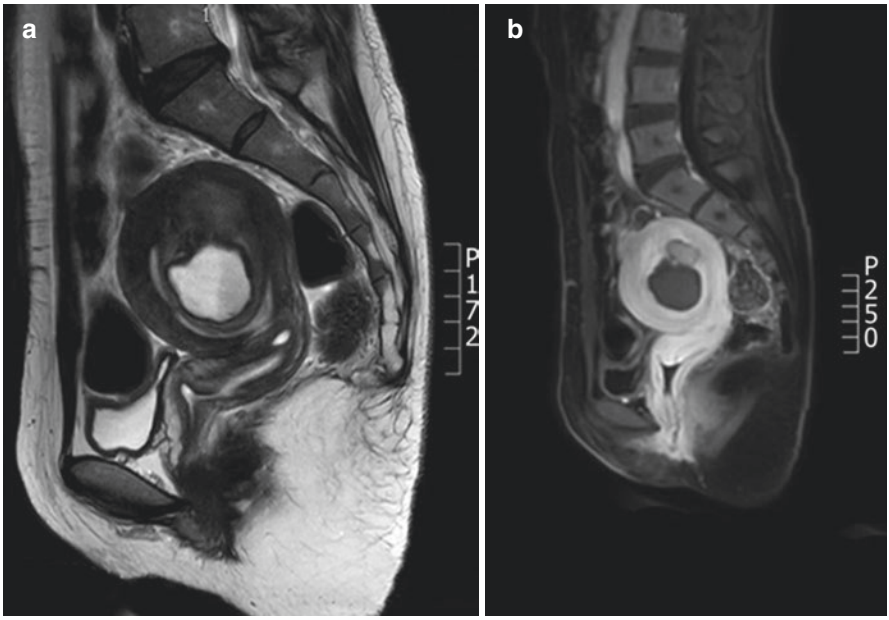

Fig. 13.2 Magnetic resonance images of cystic adenomyosis (hyperintensity in T1-weighted image, moderate to high intensity in T2-weighted image, and low intensity in the edge). A: Case 1; B, Case 2 [27]

resemble those of an endometrioma (Fig. 13.2). The cystic mass has no communication with the endometrial cavity, and surrounding capsule is visualized as a hypointensity region on T2-weighted images reflecting muscle hypertrophy compared to the remainder normal myometrium.

Although it is difficult to differentiate an isolated adenomyotic cyst from a noncommunicating uterine horn, exclusion of a congenital uterine malformation should be the primary goal of differential diagnosis. Detection of a urinary track congenital anomaly favors toward a congenital uterine malformation. Hysterosalpingography, although helpful, cannot be utilized on most adolescent girls. An intramyometrial hydrosalpinx, a hemorrhagic leiomyoma, and a hematometra with hematocolpos, in case of vaginal atresia, should be included in the differential diagnosis.

Treatment

Treatment of adenomyosis in adolescence depends on the severity of the patient's symptoms and the size and location of the disease. Medical treatment includes NSAIDs to alleviate dysmenorrhea or pelvic pain. Hormonal suppressive therapy with gonadotropin-releasing hormone (GnRH) agonists or COCP may temporarily decrease lesion's size and postpone or avoid surgical treatment. Itam et al. described

two cases of adenomyosis in young girls where successful regression of their symptoms achieved by a 6-months' course of GnRH analogues followed with COCP or COCP alone [11]. In an interesting study by Mansouri et al., hormonal suppression with either GnRH agonists or COCP in four adolescent girls achieved regression of symptoms [31]. The authors repeated the MRI in 1–2 years while on treatment, and resolution of the lesions was detected in all patients. Since only a few reports exist on medical treatment in adenomyosis in adolescence, no clear evidence can be drawn on long-term effects and efficacy of these regimens.

Since fertility preservation is paramount in these ages, surgical treatment is reserved for those cases where initial medical therapy cannot control patient's symptoms [32]. Laparoscopic cytoreductive surgery for adenomyosis is generally applied in cases of adenomyosis in adolescent patients since adenomyosis is affecting a limited part of the uterus [33, 34] (Fig. 13.3). Excision via laparotomy has been reported in a few patients [35]. Laparotomy offers the advantage of palpation and accurate localization of the lesions in cases where preoperative diagnosis is ambiguous.

During laparoscopy, accurate knowledge of the topography of the lesion is important to avoid unnecessary uterine incisions. Primary consideration in these cases is the removal of the whole of the adenomyosis, if possible, while preserving as much unaffected myometrium as possible. The serosa is cut over the lesion, and vasopressin is instilled to minimize uterine bleeding. The cystic roof is entered, and the contents removed with a suction-irrigator, followed by irrigation (Fig. 13.4). Once the whole cystic wall has been inspected, the wall of the cyst is grasped with toothed forceps and then resected from the surrounding myometrium. The main criterion on identifying the defective tissue during laparoscopy is the macroscopic appearance of the lesion. Adenomyotic tissue is paler, is less vascular, and bleeds less due to fibrosis, contrary to unaffected tissue, which is redder and more hemorrhagic (Fig. 13.5). No dead space should be left during suturing, and unnecessary use of diathermy should be avoided. In cases where the endometrial cavity has been entered, this should be closed separately [36]. The resulting incision is closed in one or two layers (Fig. 13.6). Surgical treatment ensures definite resolution of

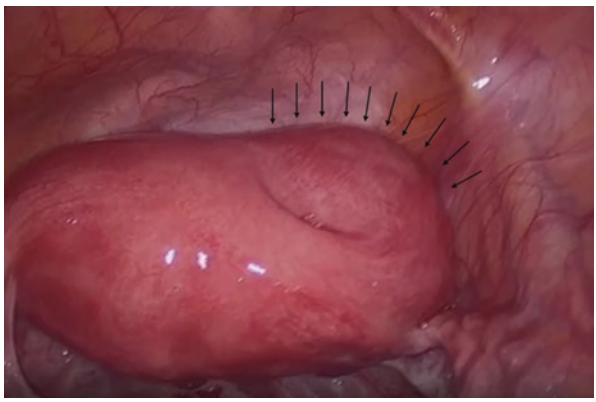

Fig. 13.3 Laparoscopic view of the uterine cystic lesion (marked with arrows) located in the right portion of the uterine fundus. The lesion represents a common location of cystic adenomyosis, just underneath the round ligament

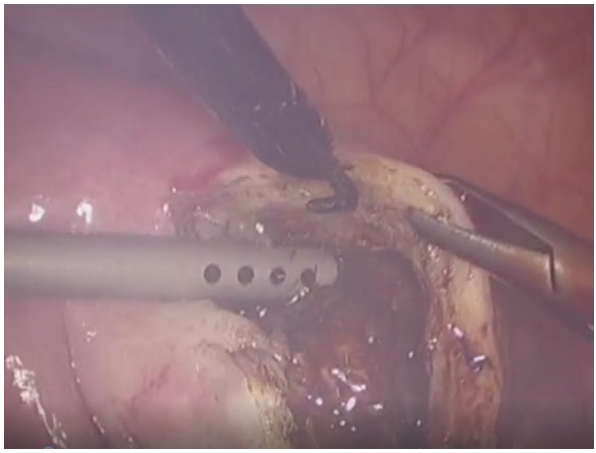

Fig. 13.4 Monopolar diathermy is commonly used to dissect the lesion. Cystic adenomyosis is filled with dark-brown fluid

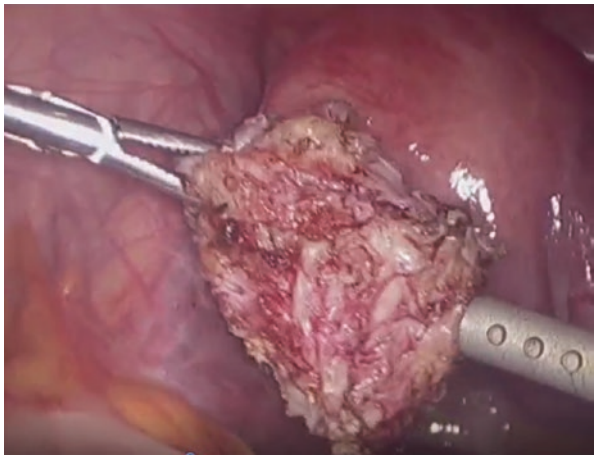

Fig. 13.5 The macroscopic appearance of the dissected lesion

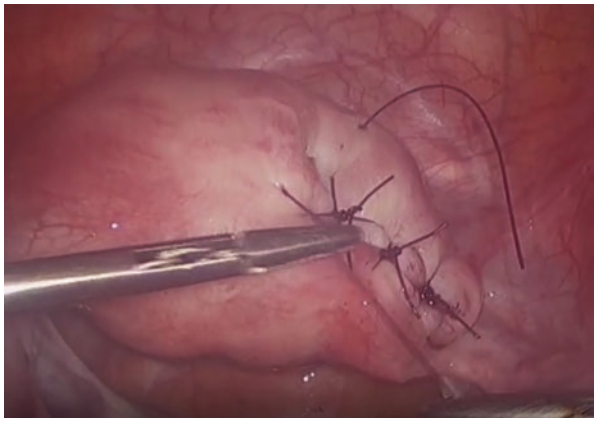

Fig. 13.6 The surgical wound is closed with deep interrupted 1-monocryl sutures in two layers

symptoms. A surgical alternative to a laparoscopic excision of adenomyosis is laparoscopic presacral neurectomy. This procedure has been introduced as a safe option for treating severe dysmenorrhea and central pelvic pain in young patients. Although the integrity of the uterus is not compromised by this technique, data on long-term efficacy in adolescent patients with adenomyosis are scarce [37, 38].

Conclusion

Adenomyosis in adolescence represents a more discrete variant of adenomyosis, typically the cystic type of the disease. Establishing a correct diagnosis and treatment requires that the gynecologist has a clear understanding of the disease and its relation to severe dysmenorrhea in young age. Similar disease entities have been described in the literature using different nomenclature, thus yielding conflicting evidence. An increased awareness of this condition is mandatory to appropriate diagnostic approach and effective treatment. Laparoscopic surgery can significantly improve the associated dysmenorrhea and increase the likelihood of future pregnancy; however, it should only be reserved for those patients whose symptoms are nonresponsive to conservative measures. Laparoscopic excision of the lesion and uterine reconstruction may be limited by the difficulty in defining the actual extent of the adenomyosis, when preoperative diagnosis is ambiguous. It requires a high degree of expertise and dedication on preserving as much healthy myometrium as possible.

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Chapter 14
Teenage Patient Story

Emma Henry and Ceana H. Nezhat

It all started in the fourth grade. Each morning, the acne-traced face in the morning greeted me with discontent. Kids ran up to me in amusement, impeding me with comments such as "What are all those red bumps on your face?" and "Is that contagious?" To this day, I cannot pin down the exact moment the acne started to progress. As far as I am concerned, one day I had a crystal clear baby face and the next, the complexion of a pepperoni pizza. Equally as bad, it seemed as though my body hair sprouted completely overnight. Being the loving, health freak she is, my mother immediately sent me to a dermatologist. Years went by, and I tried every pill, wash, acid peel, topical cream, and even laser treatment we could find.

To make matters worse, when Christmas break of sixth grade came along, I started my period. As an 11-year-old gymnast with severe acne, an overwhelmingly heavy menstrual cycle, and a mortifying amount of body hair, life was very difficult. My hormones never failed to ruin my happy and optimistic outlook on life. I had to deal with the struggles of shaving very early in my life, and I could always count on some aching whiteheads to brighten up my day. Above all, however, my periods seemed to take control of my life. For the first 6 days, I would use super plus tampons accompanied with a nice thick pad. Some days were so bad I had to stay home from middle school. Even as the other girls caught up to me and hit puberty, I always felt odd and out of place. My voice was deep, I couldn't seem to control my weight, and I had constant pain and fatigue. Doctors prescribed birth control pills to relieve my acne, but this only opened up a new world of problems. The first pill I tried made my hair fall out, leaving me with a bald spot to disguise with headbands for the next 2 years. The following prescription gave me daily migraines, making schools more difficult than ever. I eventually deserted the idea of birth control and decided it was better to suffer through the volcanoes popping up on my face without the horrid side effects I had been enduring. At my lucky time of the

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month—although there was hardly ever a full month separating them—it felt as though my insides were slowly consuming one another and ripping me open from within.

Despite the fact that I had support from my parents, I felt entirely isolated from all other girls around my age, and eventually, I developed a horrible view of my body that has permanently altered my self-image. The pain, the hair, the pimples, and my oblong figure were enough to drive me over the edge. Even so, I always told myself, "Come on, just suck it up…every girl has to go through this." Little did I know that what I was experiencing was nothing compared to the menstrual cycles that my cheerleader friends humorously complained about during locker room chats. Years went by, and with the assistance of none other than Accutane, my acne improved drastically. During this time, though, I tore my ulnar collateral ligament and underwent Tommy John surgery in June of 2016. They grafted tissue from my hamstring and constructed a new ligament for my elbow. Recovery would take a year. During that time, I swelled up like a kitchen sponge and, standing at 5′2″ at age 13, reached my peak weight of 135 pounds.

When school started the following fall, I was in eighth grade, the first year I would be a cheerleader. While cheerleading aided in shedding some of the pounds, considering I had been inactive after hanging up my leotard and quitting gymnastics, it didn't help my distorted body image, my ever-growing body hair, or my consistently worsening pain which had now spread throughout my body. My back ached constantly, along with my abdomen, chest, and even my rectum. I went to doctor after doctor in a desperate search for answers, but the only answer I received was in the form of pain medication, more specifically meloxicam. Initially, it provided some relief, but overtime, its effects weakened, and I became the cheerleader always slouching over in pain. Months and months went by before I began experiencing chest pain and horrible acid reflux. I went to my pediatrician, who confirmed that the meloxicam had blessed me with a stomach ulcer. He took me off the medicine and treated the ulcer. It was at this appointment he told me that the only other source of my pain had to be related to "female issues." I believe this is when I was at an all-time low. I had no answers, I had no relief, and I had no confidence in my body whatsoever.

Then, like a message from God, one of my mother's very best friends suggested something that neither of us had even contemplated. She recommended I see an endometriosis specialist. Although it was a long trip to Atlanta from the little town of Greenbrier, Arkansas, my parents were willing to do anything to help me. And so the journey began with my heart ready for the answer for which it had been so desperately been searching. When the time came for my first appointment, I was quite nervous, not of what would happen but of whether I would come out of that office knowing what was wrong with me. I vividly remember the nurse greeting me at the door with an ear-to-ear smile and a kind voice that led me into the office. As my parents and I sat in front of a huge desk awaiting his entrance, I said a silent prayer to myself. I begged and begged that this appointment would me different than the hundreds of useless ones I attended prior. Just as I let myself relax, the doctor

entered the room with a warm and welcoming expression on his face. Somehow, I knew right then that my life was about to change and that he was determined to see that through. The four of us discussed the timeline of all my symptoms for what seemed like hours. However, the rest of the appointment went by faster than you can say "potato salad." After having my vitals taken and undergoing a quick yet painful ultrasound, we all met in the conference room, and I finally got some answers. The specialist explained to my parents and me that I had polycystic ovarian syndrome (PCOS). He also revealed he had a high suspicious of endometriosis and that it would take surgery to confirm it. Little contemplation was needed for my parents and me to decide that we wanted to go through with the surgery, so we saved the date for a month later, June 20, 2017.

The month between the consultation and the surgery couldn't have gone by faster, and the next thing I knew I was back in Atlanta, chatting it up with the surgical coordinator about Esperanza Spalding and Chris Cornell the day before the operation. The morning of surgery was an early one. My parents and I woke up at 3 a.m. to go to the hospital. The last thing I remember before blacking out was the doctor's voice saying, "Okay, princess, we're going to take good care of you."

I woke up in immense pain. Most of it, contrary to what was expected, was throbbing in my shoulders. The nurses classified it as gas pain, but I thought my bones were on the verge of dislocating. When my parents came in the room, they informed me that I was under the knife for 4 hours. Most of the time following the operation is a complete blur. The thing I remember most clearly, though, was when the specialist entered my room and told me that he found endometriosis, and lots of it, everywhere: around my spine, ovaries, and rectum. I was more relieved to hear those words than I ever could have imagined. In that moment, I was given answers. I was given the truth. I would have broken down sobbing like a newborn had I not been immobilized with pain. I did manage quite a few tears, which I'm sure broke everyone's heart. My recovery was uneventful. It was later on during a follow-up appointment that another problem was discovered.

The specialist told me I had a fibroadenoma in my breast and a cyst the size of a tennis ball near my right ovary. No, this wasn't the best news, but these problems were fixable. I saw a breast specialist about my tumor, and it was removed in June 2018. (I know, June must be my month of surgery.) My cyst went away overtime with vitamins and a healthy diet. However, one problem still remained: digestion. I continued to have acid reflux and constipation up until September 2018 when I went to see a gastroenterologist at Children's Hospital. There, I experienced another life-changing appointment. She helped me see the reason I suffered from digestion complications was because I was putting the wrong foods in my stomach. Through books and documentaries, I decided to go on a whole-food, plant-based diet. Within weeks, I ceased taking most of my medications, and the little acne I still had vanished completely.

Today, my weight is at its best, and my self-esteem is slowly improving to what it was before I was blessed with all these wonderful difficulties. As sarcastic as that

must sound, I must insist that I am 110% serious. I see each and every part of my story as a blessing. I would not be the person I am today without the obstacles I have overcome with the support and help of my parents and my wonderful doctors. Thanks to them, I can live my life pain- and acne-free. Thanks to them, I can one day have the big, happy family I have always desired. Thanks to them, I am free from myself and free to live my life the way the Lord intended for me to do so.

Part V
Endometriosis Classifications

Chapter 15
Current Classifications Addressing Endometriosis in Adolescents Related to Symptoms

Pavan Kumar Ananth and Ceana H. Nezhat

Endometriosis is a disease with many phenotypes, and as such, its classification is challenging. Though multiple systems exist attempting to standardize descriptions of endometriosis lesions, their anatomic location, and associated pelvic adhesions, their usefulness is limited. Specifically, they do not address the adolescent population, symptoms related to endometriosis, or quality-of-life measures. It is well known that the extent of the disease seen at the time of surgery does not always correlate with the severity of symptoms a patient may experience. Thus, it is essential, as outlined by the World Endometriosis Society Consensus on the Classification of Endometriosis, that classification continues to be an area of research [1]. Staging endometriosis is important in order to create a common language, enable specificity of diagnosis, standardize comparisons, and facilitate research applications [3].

An ideal system for the classification of endometriosis based on symptoms should have the following general features:

- Provide information on the severity and type of endometriosis
- Correlate with the severity and type of symptom including pain and infertility
- Be accessible, reproducible, and easy to perform
- Provide information about the prognosis of the disease [2]

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Additional criteria for an optimal system to benefit women with endometriosis include:

- Simplicity (for doctors to explain and for women to understand)
- Ability to predict response to treatment for (i) pain and (ii) infertility and (iii) recurrence of symptoms after treatment
- An empirical and scientific base
- Comprehensiveness for all cases
- Use of unambiguously defined terms
- Reflection of the progression of disease (with scientifically derived, nonarbitrary cutoff points that are clinically meaningful)
- Having general consensus [3]

The first classification system for endometriosis was created by Sampson in 1921. He categorized hemorrhagic ovarian cysts, noted adhesions, and proposed his theory of retrograde menstruation. Acosta et al. later proposed a system based on the premise that the severity of the disease determined the success of the surgical operation. It focused on the site and distribution of lesions and emphasized adnexal adhesions as a factor in fertility. Others, such as Kistner and Buttram, also incorporated malignancy, laparoscopic findings, and therapy, but none were able to predict clinical outcomes [3].

Nezhat et al. studied the development and progression of ovarian endometriomas and devised a classification system to improve the way they are diagnosed (Table 15.1) [4–6].

The best-known and most widely used system is the revised American Society for Reproductive Medicine classification (r-ASRM). Originally proposed in 1979, it was designed to be flexible enough to describe a variety of cases, was quantitative to allow for analysis, and had an associated paper form to encourage documentation. Revisions, adapted in 1985, eliminated extensive disease stage, removed tubal endometriosis as a separate category, created a category for minimal disease, differentiated superficial vs. deep lesions of the peritoneum and ovaries, required more detail for adnexal adhesions, quantified filmy vs. dense adhesions, considered posterior cul-de-sac obliteration to be severe disease, doubled the solitary adnexa score, and recorded additional pathology [3]. It still provides a standardized form for recording pathologic findings and assigns numeric values in an effort to predict the probability of pregnancy following treatment (Fig. 15.1a and b [7]). It was, however, unable to be validated by the American Fertility Society. There were apparent trends, but the scoring system was not found to be a sensitive predictor of fertility, and there is poor correlation between extent of disease and pelvic pain. Proponents of the r-ASRM classification cite its ability to provide clear and reliable documentation of the extent and location of the disease. There are certain subjective elements with potential for observer error, but many health-care providers continue to use the staging system to describe the severity of the disease [3–8].

The Enzian classification, published in 2005, specifically addresses deeply infiltrating endometriosis and is often used as an adjunct to the r-ASRM score to account for the involvement of retroperitoneal structures and nongynecologic

Table 15.1 Classification of ovarian endometriomas, Nezhat et al.

Type I: Primary endometrioma—True endometrioma origin, similar to that found on peritoneal surfaces. These "pure" endometriomas are characterized as small superficial cysts containing dark "chocolate" fluid. As these endometriomas develop on the surface of the ovary, they are typically found to be firmly adherent to the tissue and difficult to remove surgically. Histological analysis always reveals only endometrial glands and stroma.		
Type II: Secondary endometrioma—Follicular or luteal ovarian cysts have been involved or invaded by cortical endometriotic implants or by primary endometrioma. Further distinction between three types of secondary endometriomas based on the relationship of cortical endometriosis with the cyst wall		
Type IIa: Endometriomas are usually large and with a capsule that is easily separated from the ovarian tissue. If endometrial implants are seen, they do not penetrate the cyst wall. Upon histological examination, the walls are found to be clear of any endometrial tissue. These hemorrhagic cysts are either follicular or luteal in origin.	*Type IIb:* Endometriomas have features of functional cysts but show deep involvement with surface endometriosis. The lining of these cysts is easily separated from the ovarian capsule and stroma, except adjacent to the area of endometriosis, where the ovarian capsule has adhered to the cyst wall. Histological findings reveal endometriosis implants in the cyst wall.	*Type IIIc:* Endometriomas are similar to the former type as these functional cysts show extensive surface endometrial implants. However, these ovarian cysts show deep penetration of the endometriosis into the cyst wall, spreading to at least one area of the ovarian capsule. The basis for differentiating between the type IIb and type IIc cysts is, thus, the degree of invasion of the endometriosis into the cyst wall. This characteristic can be distinguished clinically by the progressive difficulty in removing the cyst's capsule. A high degree of correlation was observed between the clinical findings regarding the presence of dense adhesions and the histological evidence of endometriotic extension into the wall of the ovarian cyst.

organs [9]. The Enzian classification was revised in 2011 in an effort to simplify it and reduce the amount of overlap with the r-ASRM (Fig. 15.2) [10]. There is a clear correlation between these two scoring systems that are generally accepted as complementary [11]. Additional strengths of the Enzian classification include partial correlation between lesion locations and clinical symptoms as well as severity grades substantial association with pain and dysmenorrhea symptoms [12]. This is a unique achievement of the Enzian classification system compared to others. Preliminary data suggests mathematical models can be created based on this classification allowing for a fairly accurate estimation of the operating time needed for surgical management in select cases, with a standard deviation of 35.35 minutes. In theory, this could improve preoperative surgical planning and patient counseling [13]. Commonly cited reasons for its poor acceptance by gynecologists are the complexity of its documentation and the absence of significant factors such as pain or infertility in the system [3].

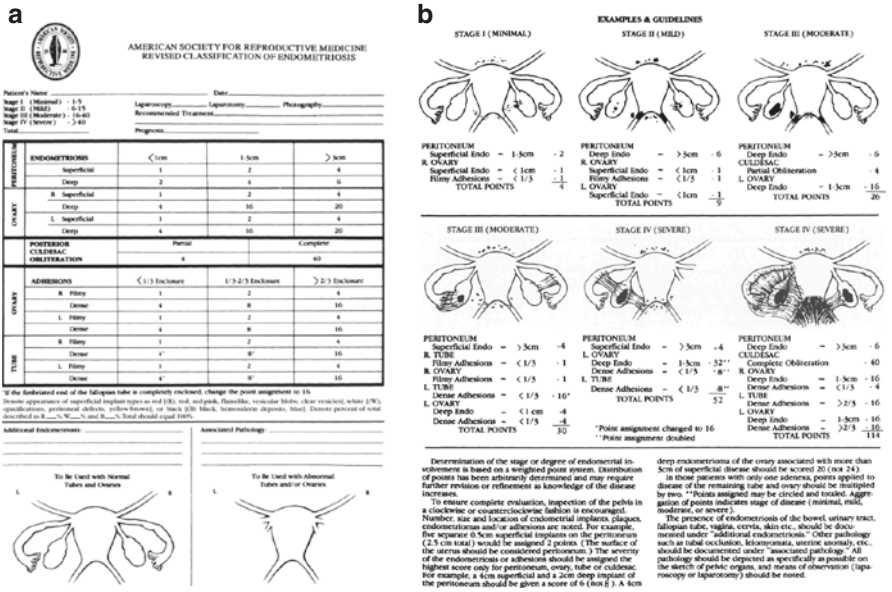

Fig. 15.1 (**a**) and (**b**) Revised ASRM classification [7]

The only validated endometriosis classification to date is the endometriosis fertility index (EFI), created by Adamson and Pasta and first presented in 2008 at the tenth World Congress on Endometriosis in Melbourne, Australia. It provides clinically useful information for patients with surgically confirmed endometriosis attempting non-IVF conception [14]. Factors used to create this prognostic score include the functional status of each ovary, fallopian tube, and fimbria, derived by intraoperative assessment, as well as historical factors such as the patient's age, number of years of infertility, and previous pregnancies, in conjunction with the patient's AFS score (now known as the r-ASRM score) [2].

EFI has good correlation with spontaneous pregnancy rates as it includes important clinical variables which affect the likelihood of pregnancy independent of the presence of endometriosis. Drawbacks are it requires surgical staging, does not consider uterine abnormalities, and does not correlate with pain symptoms [2]. Subjectivity of the least function score was shown by sensitivity analysis to be far less variable than one might assume [3]. Furthermore, the EFI can be used to help guide patient management after endometriosis surgery with regard to treatment options, duration, and cost prior to considering assisted reproductive technologies (ART). Patients with a good prognosis can be reassured while avoiding expensive and invasive procedures, and those with a poor prognosis can bypass potentially unsuccessful management options, thereby preventing wasted time, which can be critical in patients with infertility [3]. Finally, in patients with endometriosis-associated infertility, EFI scores appear to be more useful than r-ASRM stage [15].

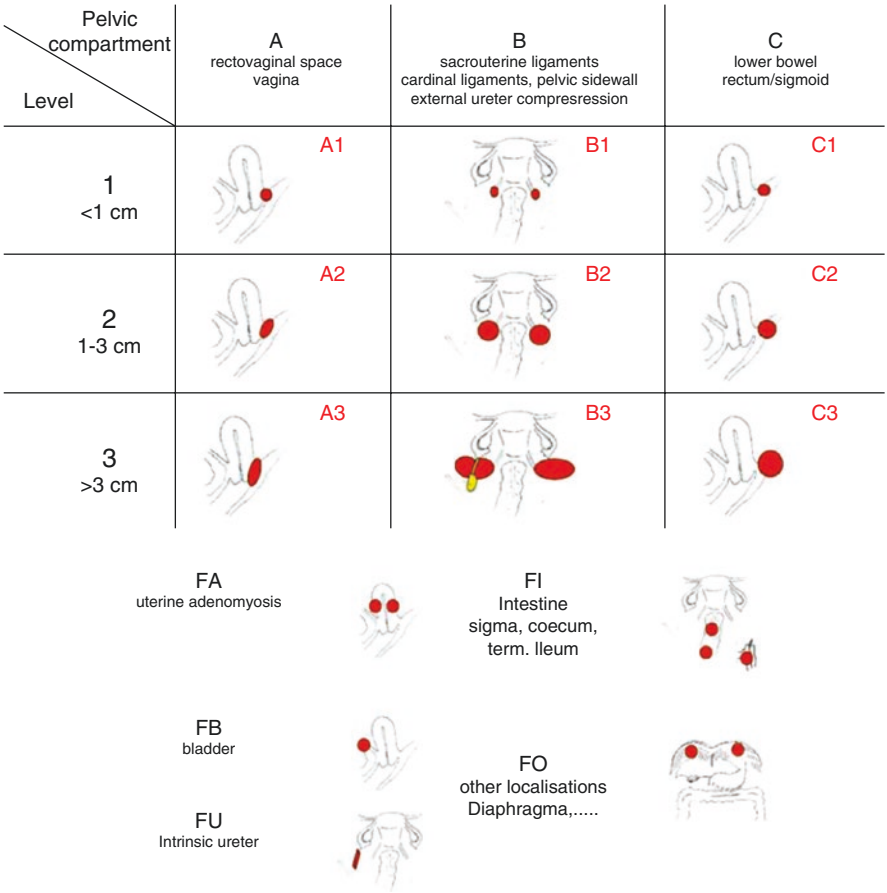

Fig. 15.2 The revised Enzian classification [10]

Newer classification systems are continuously being created. One recent proposal from Koninckx et al. in 2011 adds adenomyosis, peritoneal pocket lesions, and subtle endometriosis as three more "classic" phenotypes (typical or peritoneal, cystic, and deep) and places more emphasis on the size of the lesions [16]. This is a significant advancement as endometriosis not only has many different clinical manifestations, it also has a variety of histologic manifestations that are not addressed by current classification systems. These include adenomyosis (acknowledged by Koninckx et al., as mentioned above), endosalpingiosis, atypical endometriosis, embryonic cell types, and malignancy arising from endometriosis. Though endosalpingiosis is sometimes considered to be a distinct histopathologic entity, distinguished by a lack of endometrial stroma as compared with classically defined endometriosis, its close association with endometriosis and chronic pelvic pain is well documented in the literature. Women with endosalpingiosis are significantly

more likely to be diagnosed with endometriosis, and the anatomic distribution of these lesions in patients with chronic pelvic pain is consistent with that seen in endometriosis [12]. Atypical endometriosis is known to be a precursor lesion to ovarian cancer and requires special attention, as does endometriosis that occurs concomitantly with malignancy, as this likely represents a spectrum of disease [12]. Somatic stem cell dysfunction is also a rare but recognized entity that is sometimes noted histologically but requires more research to understand its clinical significance [12].

The AAGL (formerly referred to as the American Association of Gynecological Laparoscopists) also initiated a project in 2007 to develop a tabulation system rather than a classification to document endometriosis found at the time of surgery. Theoretically, they reasoned once the disease can be accurately described, a clinically useful classification system could be developed from an analysis of the descriptions. They then utilized the opinion of several endometriosis experts to create a weighted score based on different anatomical factors with respect to pain and infertility symptoms. A special interest group is now proposing a classification system to stratify surgical difficulty into four levels:

1. Level 1: Excision or desiccation of superficial implants and simple, thin, avascular adhesions
2. Level 2: Stripping of ovarian endometriomas; appendectomy; deep endometriosis not involving the vagina, bladder (not requiring suture), bowel, or ureter; dense adhesions not involving the bowel and/or ureter.
3. Level 3: Dense adhesions involving the bowel and/or ureter; bladder surgery requiring suture; ureterolysis; bowel surgery without resection (shaving)
4. Level 4: Bowel resection with end-to-end anastomosis; ureteral reimplantation or anastomosis

Preliminary results have been reported to correlate with pain, infertility, and surgical difficulty. While correlation with pain seems to be better as compared with other systems, it has not been shown to predict pregnancy rates in endometriosis patients with infertility [3, 17]. Other systems are even more specific; Knabben et al. have proposed one exclusively for the categorization of ureteral endometriosis [18].

Some authors believe it is impossible for one classification system to appropriately address all of the relevant issues associated with this disease. Khazali writes:

> The more we understand endometriosis, the clearer it becomes that the highly complex nature of the disease defies a single all-encompassing classification system. Perhaps a system that accurately describes the surgical findings, whilst correlating with symptoms and predicting fertility outcomes cannot exist as the pathophysiology of the disease and the ways it causes its multitude of symptoms are convoluted. The success of EFI is due to its narrow scope and the fact that it doesn't aim to solve all the problems at the same time. Therefore, a similar approach is needed to devise a system that limits itself to describing the surgical findings; without attempting to correlate with symptoms or fertility outcomes [19].

It is clear this area requires significant research. Endometriosis associated with pain in adolescents has been extensively reported, but diagnosis is often delayed. In some

studies, the average time between onset of symptoms and diagnosis was almost 2 years and required three physicians for pain evaluation before reaching a diagnosis [20]. About two-thirds of adolescents with chronic pelvic pain or dysmenorrhea are found to have endometriosis on laparoscopy, and about one-third of these are categorized as having moderate to severe disease by the r-ASRM classification [21]. Pelvic pain in these patients has been shown to significantly affect quality of life due to interference with work and school, daily activities, exercise, and sleep [22].

Adolescents are a very important population that appears to have been neglected when it comes to endometriosis classification. The development of a system that focuses on pain is essential as it is one of the most common and debilitating symptoms in this age group. Once a validated and universal language is developed to describe endometriosis in adolescents and its associated symptoms, further research could be streamlined to advance our knowledge and improve management and outcomes.

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Part VI
Imaging

Chapter 16
Imaging for Endometriosis in Adolescents

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Introduction

For the first time in 2018, national guidelines [1] were introduced related to the concept of pelvic imaging with ultrasonography, regardless of findings on pelvic examination; this information should be considered during evaluation for secondary dysmenorrhea. As a matter of fact, ESHRE [2] and NICE [3] guidelines avoid to specify a possible role of imaging in the diagnosis of endometriosis in younger patients.

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Unfortunately, no specific study focusing on the diagnosis via imaging of endometriosis in adolescent exists in the literature. Using only laparoscopy as a diagnostic tool results in a delay in diagnosis of endometriosis and should be considered, especially for young women with pelvic pain (the median delay is reported to be 12.1 years in women aged ≤19 years) [4]. Nezhat et al. found patients ($n = 25$) with a mean age of 17.2 had experienced symptoms for an average of 22.8 months and seen a median number of three physicians before receiving an accurate diagnosis [5]. On the other hand, endometriosis *has* to be considered as a possible diagnosis in adolescents with suggestive symptoms because most women diagnosed with endometriosis date the onset of their symptoms to their teens [6].

Wright and Laufer [7] published a case report of an endometrioma in an 18-year-old adolescent; some authors [8] identified the presence of endometrioma in 6% of cases of adnexal masses in a large population of 521 patients with an ovarian cyst less than 20 years of age. Lee at al. [9] in a report on 35 patients less than 20 years report that adolescents with endometrioma(s) experience more frequent pain (77%) compared to adult women, but other clinical characteristics are similar. In addition, the same authors [8] found that in 57% of cases, pouch of Douglas obliteration was present associated with the endometrioma in the absence of deep endometriosis. Moreover, there was no difference in the presence of various lesions such as peritoneal endometriosis, posterior cul-de-sac obliteration (>50%), tubal or ovarian adhesion, and deep endometriosis according to age [9]. These results are not expected in an apparently progressive disease as proposed by Unger and Laufer [10] that found an advancement of disease in absence of treatment.

Özyer S et al. [11] evaluating 63 adolescents and young women (with less than 24 years of age) with an endometrioma found chronic pelvic pain to be the most common symptom (44%); the mean diameter of an endometrioma was 47 mm in the left ovary and 50 mm in the right ovary. Moreover, 14 (22%) had an associated presence of deep endometriosis (apparently in contrast with Lee et al. [9]) and a partial pouch of Douglas obliteration in 18%. Also, other authors found the presence of more severe forms of endometriosis in young patients. Yang et al. [12] in a retrospective analysis of 63 cases found that ovaries were involved in 88% of cases, rectovaginal pouch was involved in 29%, and the uterosacral ligaments were involved in 33%. Smorgick N et al. [13] in 86 adolescents and young women (≤22 y) who underwent surgery for endometriosis found an advanced stage endometriosis (stage III or IV) in the 23% of cases. Audebert et al. [14] in a series of 55 adolescents with pelvic pain who underwent laparoscopy found endometriomas in 33% of cases and deep infiltrating endometriosis (DIE) in 11%.

Janssen et al. concluded [15] that one-third of adolescents with endometriosis at laparoscopy have moderate to severe disease. This unexpected relatively high prevalence suggests a detailed ultrasonographic scan should be proposed in the adolescent and young adult patient with clinical suspicion for the presence of endometriosis. In addition, young patients showed the presence of not only a particular form of adenomyosis [16] called uterine cystic adenomyosis but also other forms of adenomyosis [17–18] easy to identify using imaging [19, 20].

For these reasons, a less invasive approach should be suggested, and the imaging should have a key role in patients with continued pelvic pain. We based this assumption on the following findings:

1. The endometrioma represents 6% of adnexal masses in young patients [8].
2. An association with endometrioma and POD occlusion is present in 20% of young patients [11].
3. An association with endometrioma and DIE in young patients is high (22%) [11].
4. The presence of adenomyosis in young patients is reported [18].

All these findings can be correctly investigated using imaging and, in particular, transvaginal or transrectal ultrasound. Recently, a consensus has evaluated these findings in a detailed examination scan. This consensus statement on the systematic approach to sonographic evaluation of the pelvis in women with a clinical suspicion of endometriosis was published in 2016 by the International Deep Endometriosis Analysis (IDEA) [21] group with the contribution of clinicians, gynecological sonologists, advanced laparoscopic surgeons, and radiologists. The primary aim of IDEA consensus was to standardize terminology, definition of anatomy, measurements of sonographic features, and nomenclature of endometriosis lesions. The systematic US approach proposed by IDEA group includes four basic steps [21]. *The first step* is a routine evaluation of uterus and adnexa aimed to identify the sonographic signs of adenomyosis and/or presence or absence of endometrioma. The *second step* is an evaluation of transvaginal sonographic "soft markers" (i.e., site-specific tenderness and ovarian mobility). The *third step* is an assessment of status of POD using real-time ultrasound-based "sliding sign." Finally, the *fourth step* is an assessment for DIE nodules in anterior and posterior compartments. We describe related details in this chapter.

Evaluation of Adenomyosis

The uterus of young girls can show the presence of a lesion related to endometriosis, the cystic adenomyoma, that although rare may be considered when severe dysmenorrhea is associated with uterine cyst diagnosed by ultrasound and/or MRI [21–23]. The use of radiological imaging modalities enables a noninvasive and a conservative approach to this disease evaluation and management, which is particularly important in pediatric population. Branquinho et al. [23] described at ultrasound this disease entity as round mass in the uterine wall, with no apparent communication to the endometrial cavity. The Doppler study showed lesions involving wall vascularity and unremarkable blood flow to the uterus and ovaries [23]. The differential diagnosis can be a hemorrhagic and degenerative leiomyoma, uterine fibroid with fatty degeneration, isolated congenital anomaly with hematometra in a noncommunicating horn, congenital uterine cyst, and intramyometrial hydrosalpinx [23]. The cyclic nature of symptoms, ultrasound appearance, similarity of the lesion and endometrium in MRI signal intensity, and response to hormone suppression are

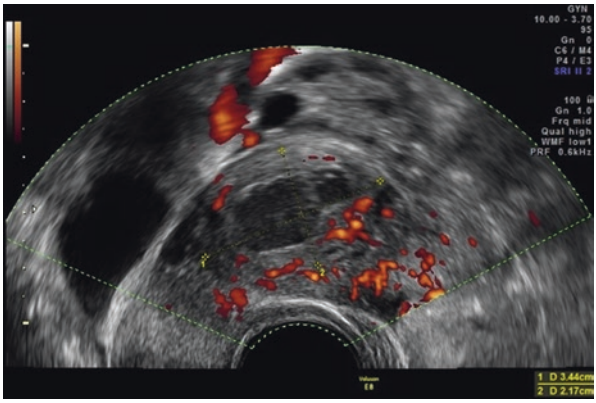

Fig. 16.1 Cystic juvenile adenomyosis in a 20-year-old patient with severe pelvic pain at color Doppler

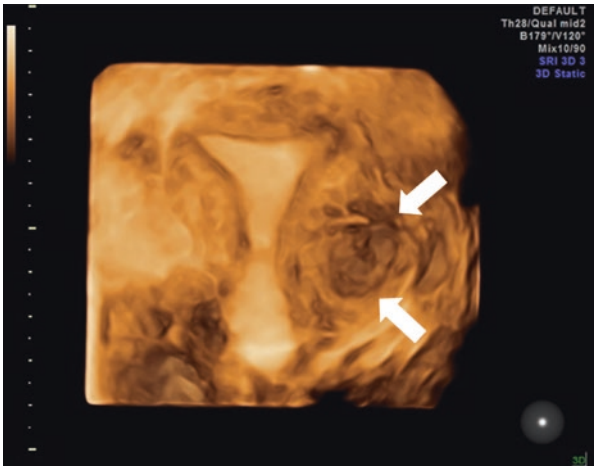

Fig. 16.2 Cystic juvenile adenomyosis in a 20-year-old patient with severe pelvic pain at three-dimensional ultrasonography rendering (arrows)

all consistent with this diagnosis [23]. When this suspicion is present, transvaginal or transrectal ultrasonography with the additional use of three-dimensional ultrasonography (Fig. 16.1 and 16.2; Video 16.1) should be considered.

Evaluation of the Ovary

The typical US appearance (transabdominal, transvaginal, and transrectal) of *endometrioma* is a cystic lesion with "ground glass" echogenicity (low-level homogeneous echogenic content corresponding to blood within the cystic cavity), well defined from the surrounding ovarian parenchyma, with no papillary projections or vascularized solid areas [24–30] (Figs. 16.3, 16.4, and 16.5). Less typical features include multiple locules (about 85% with <5 locules) (Fig. 16.6), hyperechoic wall foci, cystic-solid lesion (about 15%), and rarely solid lesion (1%) [24–30].

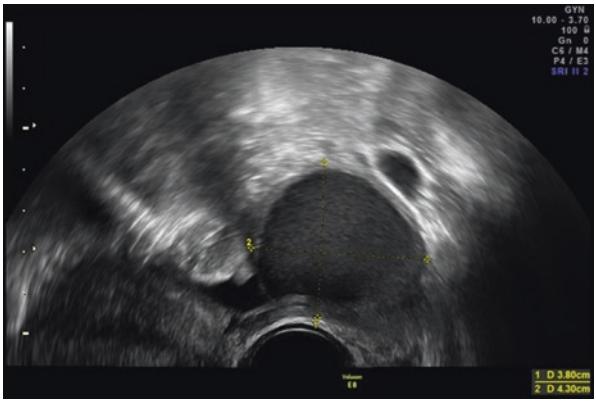

Fig. 16.3 A typical endometrioma in a 20-year-old patient with severe pelvic pain

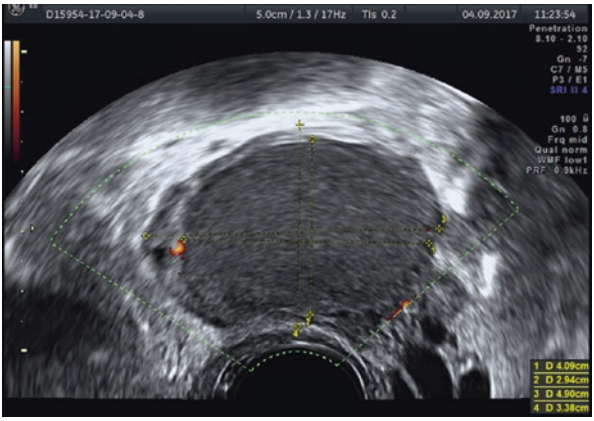

Fig. 16.4 A typical endometrioma in another 20-year-old patient

Obviously, also magnetic resonance (MR) can be used with high accuracy but in uncertain or negative cases at ultrasound (Figs. 16.4, 16.5, 16.6, 16.7, 16.8, and 16.9).

Opinions include the following: endometriomas can be confidently and correctly diagnosed with transvaginal ultrasound [24–30] and surgery is no longer considered necessary to confirm the diagnosis [31–33]. Guerriero et al. [34] investigated if sonographic characteristics of ovarian endometriomas may vary with age of women. They observed that in a population of 1005 histologically confirmed endometriomas, 78 (8%) were identified in young patients (18–24 years). Tender mass on scan became less common with increasing age, with 46% of 18 to 24 year-old women reporting tender mass on scan compared with 27% of women ≥45 years old (Table 16.1). On the contrary, the mean diameter was similar in the different age of the women, about 50 mm (Fig. 16.10). Unilocular cysts became less common with increasing age, whereas multilocular cysts and cysts with solid components became more common (Table 16.1). In 18- to 24-year-old women, 76% of endometriomas were unilocular, 14% were multilocular, and 10% had solid components. Ground glass echogenicity of cyst fluid became less common with increasing age, in

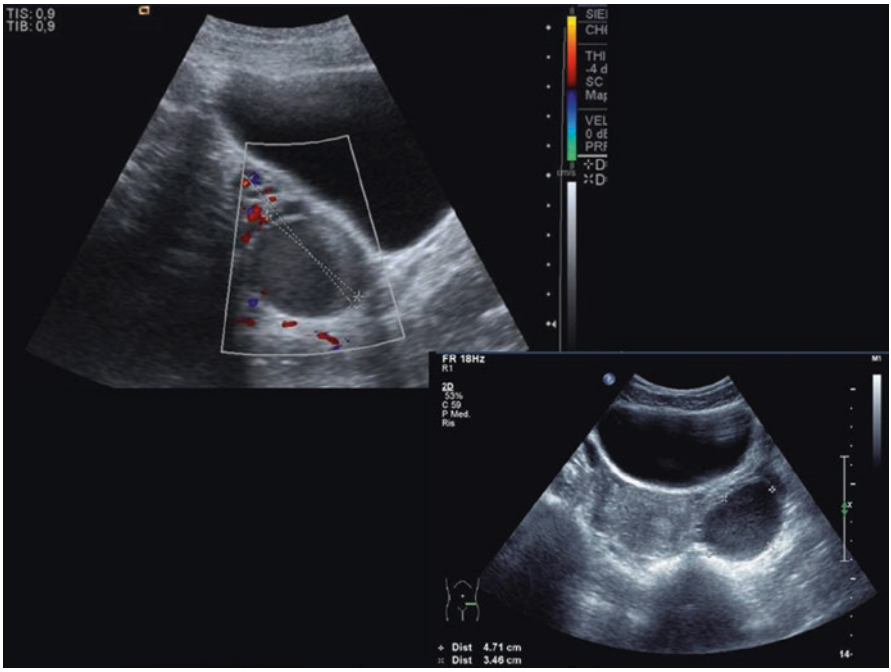

Fig. 16.5 An endometrioma in an 18-year-old girl at transabdominal ultrasound

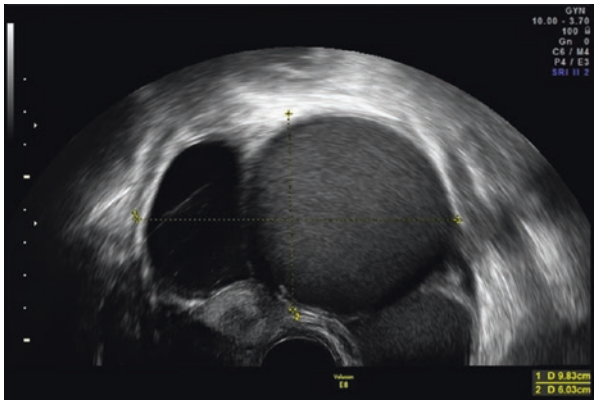

Fig. 16.6 A multilocular endometrioma in a 20-year-old patient

particular after 35 years (Table 16.2). In 18- to 24-year-old women, 77% of the endometriomas contained cyst fluid with ground glass echogenicity, 12% contained cyst fluid with homogeneous low-level echogenicity, and 12% manifested other echogenicity of cyst contents (Table 16.2) [34]. Endometriomas with papillations were less common in younger women, but the color score was similar (Fig. 16.10). Table 16.3 shows the diagnostic performance with regard to endometriomas of subjective assessment of ultrasound images in relation to patient's age. Subjective

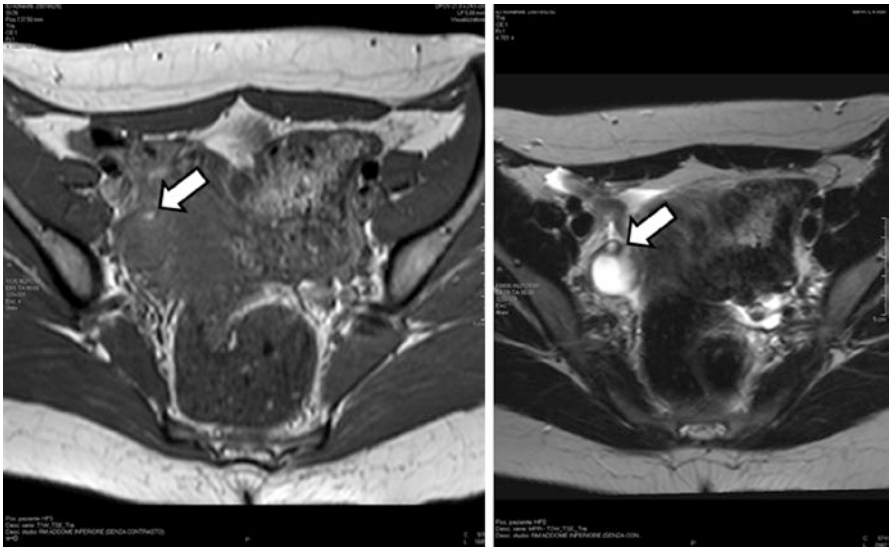

Fig. 16.7 An endometrioma at MR in an 18-year-old girl with negative ultrasound

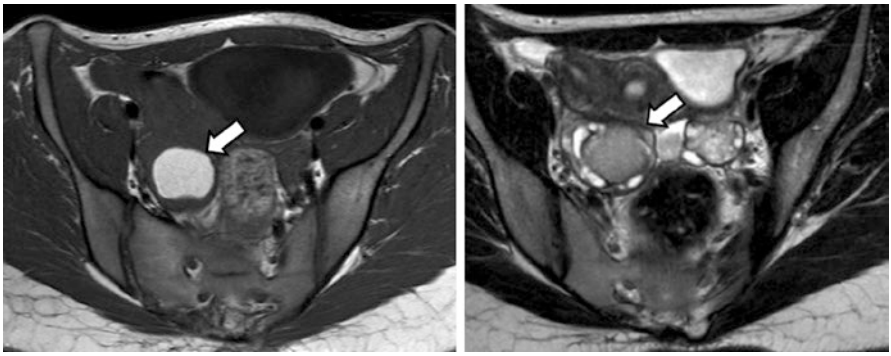

Fig. 16.8 An endometrioma and peritoneal endometriosis at MR in a 17-year-old adolescent

assessment performed best for patients below 30 years of age. The accuracy of ultrasound is very high in young patients with a sensitivity of 90% and a specificity of 97% (Table 16.3).

After the visualization of the ovary, it is inherent to evaluate position of the ovaries. This second step is a dynamic evaluation of sonographic "soft markers," site-specific tenderness, and ovarian fixation to the uterus [21, 35]. These "soft markers" are sonographic features that indirectly suggest the presence of endometriosis (Fig. 16.11). By applying pressure between the uterus and ovary, the US operator can evaluate if the ovary is fixed to the uterus, to the lateral pelvic sidewall, or to the uterosacral ligaments (Figs. 16.11 and 16.12). Also, the marker of "kissing ovaries sign" reflects the presence of severe pelvic adhesions (Video 16.2).

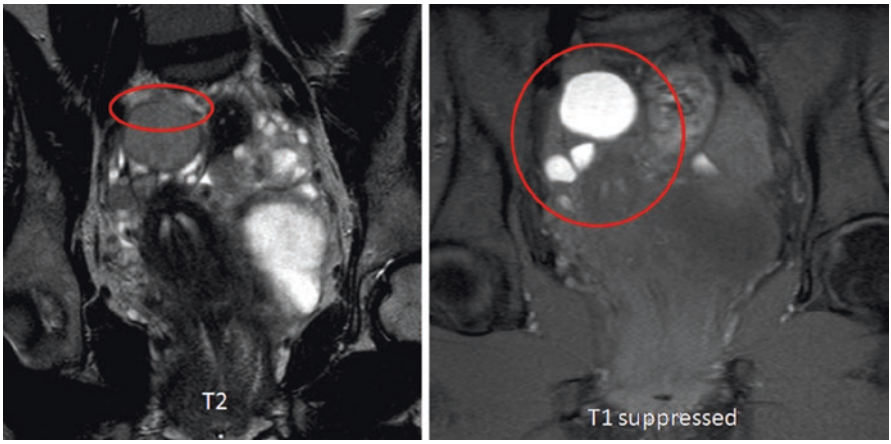

Fig. 16.9 An endometrioma and peritoneal endometriosis at MR in a 17-year-old adolescent

Table 16.1 The presence of tenderness and different cystic appearance in relation to patient's age

	Age categories (years)					
	18–24 yrs. *N* = 78 (8%)	25–29 yrs. *N* = 201 (20%)	30–34 yrs. *N* = 233 (23%)	35–39 yrs. *N* = 185 (18%)	40–44 yrs. *N* = 158 (16%)	≥45 yrs. *N* = 150 (15%)
Tender mass on scan	36 (46%)	81 (40%)	93 (40%)	67 (36%)	48 (30%)	41 (27%)
Type of tumor						
Unilocular	59 (76%)	143 (71%)	165 (71%)	128 (69%)	94 (59%)	76 (51%)
Unilocular-solid	3 (4%)	12 (6%)	16 (7%)	12 (6%)	11 (7%)	17 (11%)
Multilocular	11 (14%)	37 (18%)	42 (18%)	31 (17%)	39 (25%)	41 (27%)
Multilocular-solid	3 (4%)	6 (3%)	9 (4%)	12 (6%)	12 (8%)	14 (9%)

From Guerriero et al. [34] with permission

Sonographic evaluation can aid in the identification of other neoplasms involving the ovaries. Nezhat et al. reported bimanual pelvic examination and transvaginal sonography are equally accurate in detecting endometriosis and complement visual confirmation. When the uterine surface and ovaries are involved, transvaginal sonography is preferred [36]. Although chance of malignancy with endometriomas is low, it is not zero. In a series of 1011 women undergoing laparoscopy for adnexal mass, four were diagnosed with ovarian cancer (stages I to III) [37].

Evaluation of Pouch of Douglas

The dynamic real-time US technique to study the POD assessing the presence of "sliding sign" is an important new tool. There are two distinct techniques depending on the orientation of the uterus [21, 38, 39]. When the uterus is anteverted, we can

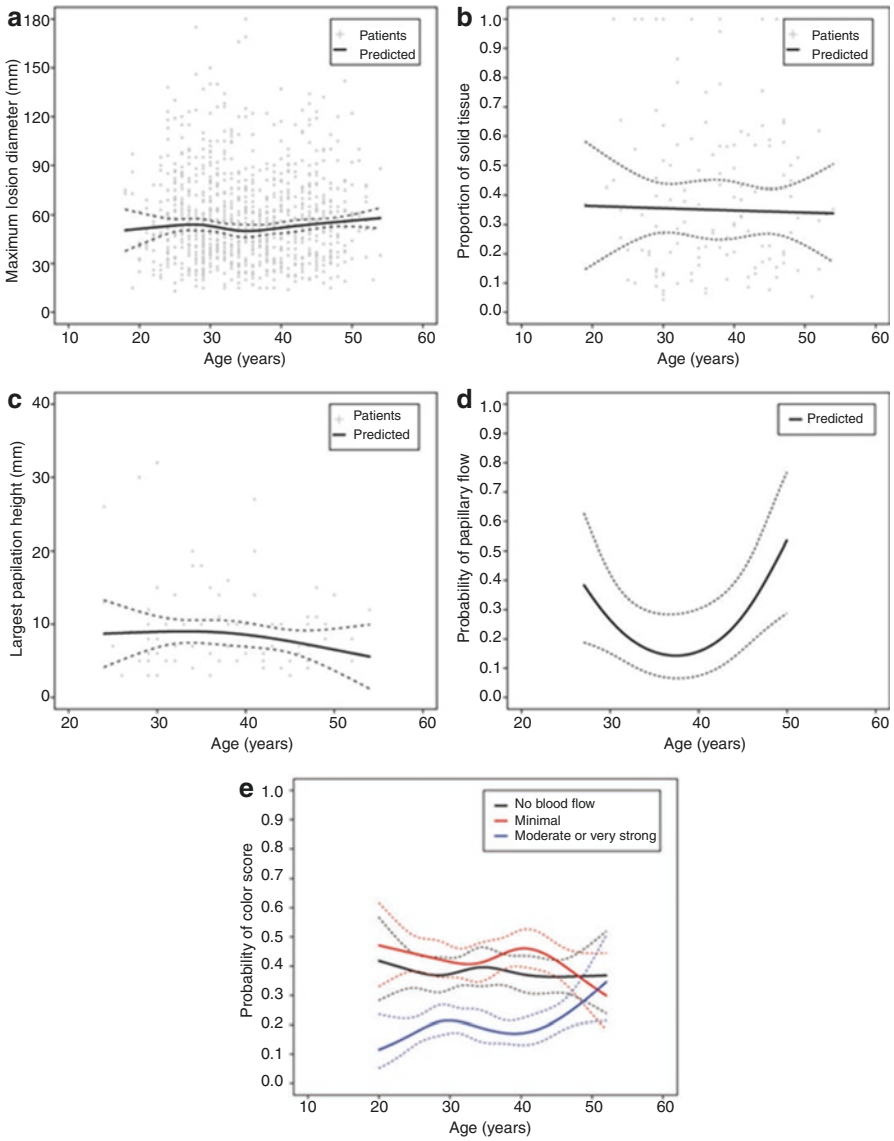

Fig. 16.10 Visualization of relationship between age and largest diameter of lesion (**a**), proportion of solid tissue (**b**), height of largest papillation (**c**), blood flow within papillary structures, (**d**) and color score (**e**). (From Guerriero et al. [33] with permission)

assess that the "sliding sign" is present if the anterior rectal wall glides on the posterior cervical wall and the vaginal wall following the application of gentle pressure with the TVS probe on the cervix. If this free sliding does not occur, we can assess that the "sliding sign" is absent in the retrocervical region. Then, we can evaluate if

Table 16.2 The different cystic content in relation to patient's age

	Age categories (years)					
	18–24 yrs. *N* = 78 (8%)	25–29 yrs. *N* = 201 (20%)	30–34 yrs. *N* = 233 (23%)	35–39 yrs. *N* = 185 (18%)	40–44 yrs. *N* = 158 (16%)	≥45 yrs. *N* = 150 (15%)
Echogenicity						
Anechoic	2 (3%)	6 (3%)	4 (2%)	6 (3%)	8 (5%)	16(11%)
Homogeneous low level	9 (12%)	17 (8%)	31 (13%)	21 (11%)	23 (15%)	26(17%)
Ground glass	60 (77%)	162 (81%)	187 (80%)	140(76%)	111(70%)	93(62%)
Hemorrhagic	2 (3%)	4 (2%)	1 (0%)	3 (2%)	6 (4%)	2 (1%)
Mixed	3 (4%)	9 (4%)	9 (4%)	13 (7%)	8 (5%)	11 (7%)
No cyst fluid	2 (3%)	3 (1%)	1 (0%)	2 (1%)	2 (1%)	2 (1%)

From Guerriero et al. [34] with permission

Table 16.3 Diagnostic performance with regard to diagnosing endometrioma of subjective assessment of ultrasound images in relation to patient's age

	Age group (years)						
	18–24 *N* = 31701 (9%)	25–29 *N* = 475 (14%)	30–34 *N* = 546 (16%)	35–39 *N* = 590 (17%)	40–44 *N* = 611 (18%)	≥45 *N* = 880 (26%)	Total population *N* = 3419
Prevalence of endometrioma	25%	42%	43%	31%	26%	17%	29%
Subjective impression of endometrioma	24%	40%	43%	30%	22%	14%	27%
Sensitivity	90%	90%	91%	85%	73%	70%	84%
Specificity	97%	97%	93%	95%	96%	98%	96%
PPV	91%	95%	91%	89%	87%	86%	90%
NPV	97%	93%	94%	93%	91%	94%	93%
LR+	30.64	27.26	13.63	18.20	19.40	30.06	22.45
LR−	0.11	0.11	0.09	0.15	0.28	0.31	0.17

This analysis includes all 3419 premenopausal patients at least 18 years old in IOTA phases 1, 1b, 2, and 3
From Guerriero et al. [34] with permission

the bowel walls glide freely on the posterior uterine wall (presence of the "sliding sign") when we press gently with the free hand on the lower abdominal wall of the patient to try to move the uterus [21, 38, 39]. We can define the POD as "obliterated" if in the posterior compartment (in the retrocervical region and/or in the retrouterine region) the "sliding sign" is negative.

When the uterus is retroverted, to evaluate the presence of the "sliding sign," we can gently press with the TVS probe on the posterior uterine wall to try to slide the anterior rectal wall on the uterine wall; if this occurs, the "sliding sign" is considered to be present. Subsequently, trying to ballot the uterus pressing with the free hand on the lower abdominal wall of the patient, we can assess if the anterior bowel wall slides on the uterine wall (positive "sliding sign"). The POD is considered as

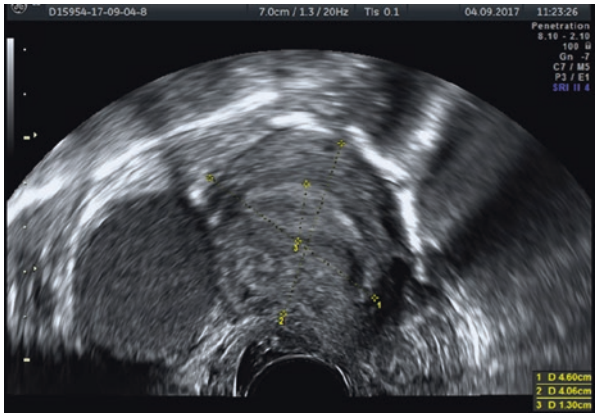

Fig. 16.11 An endometrioma in a 20-year-old patient fixed to the uterus

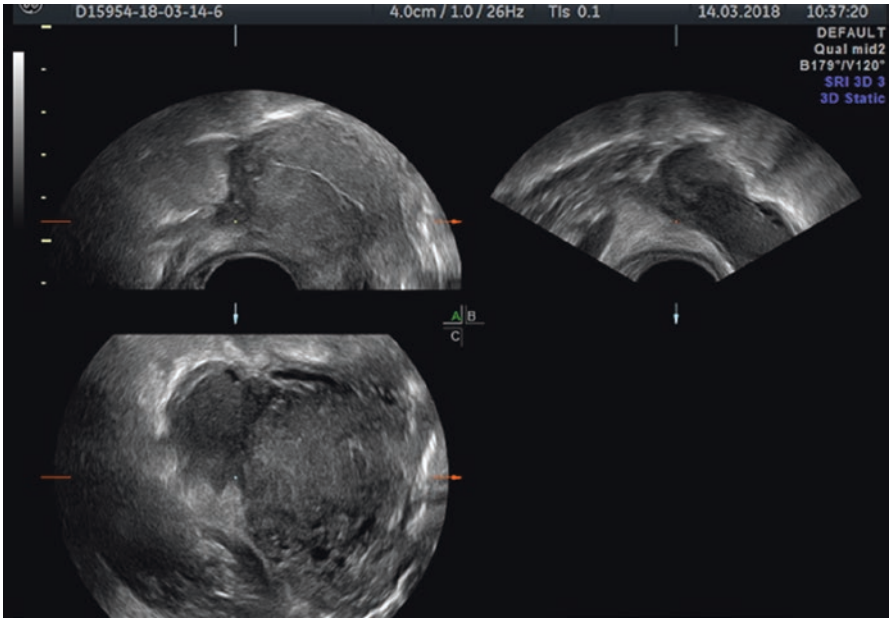

Fig. 16.12 A three-dimensional ultrasonography of an endometrioma in a 20-year-old patient fixed to the uterus

"obliterated" if this sign is negative in the posterior uterine wall and/or in the lower uterine segment [21, 38, 39] (Fig. 16.13).

The preoperative evaluation of the TVS sliding sign is an easy method to assess pelvic adhesions and/or the presence of endometriosis in the posterior compartment and to assess the obliteration of POD with a high sensitivity and specificity, respectively, of 72% and 97% [38, 39].

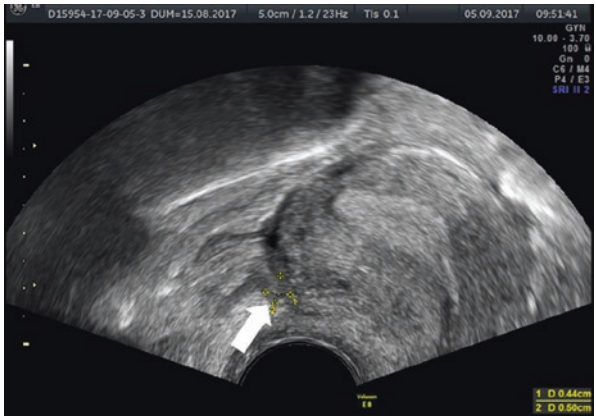

Fig. 16.13 An occluded pouch of Douglas in a 20-year-old patient for the presence of an endometriotic nodule

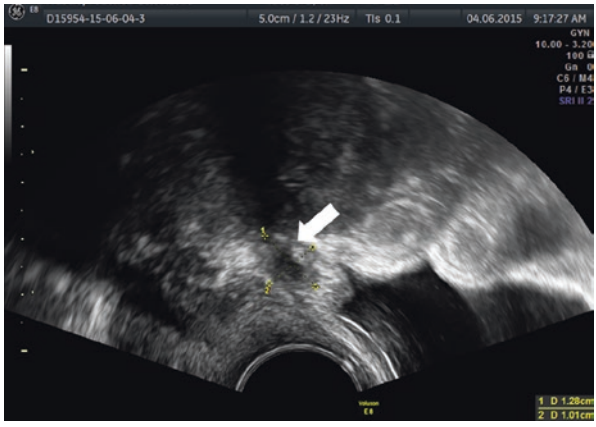

Fig. 16.14 An endometriotic nodule of the bladder wall at ultrasonography

Evaluation of Pelvic Deep Infiltrating endometriosis (DIE)

The operator should look for DIE nodules in the anterior and posterior compartments using the IDEA consensus [21]. Uterus, urinary bladder, and uterovesical pouch form the *anterior compartment*. According to IDEA consensus [20], to evaluate this region, the US examiner should place the TVS probe in the anterior vaginal fornix, and it is required to not completely empty the bladder (100–150 mL of urine). The DIE lesion involving the bladder can appear as a hypoechoic linear or spherical lesion [40–42] (Fig. 16.14), with or without uterovesical adhesions, which are evaluated using the method of "sliding sign" [21].

To assess the presence of DIE in the posterior compartment [40–44], placing the TVS probe in the posterior vaginal fornix, the US examiner should search for DIE (often as hypoechoic, not compressible, and avascular lesions) in the rectovaginal septum (RVS), posterior vaginal fornix, POD/retrocervix, anterior rectal wall/rectosigmoid wall, and para-rectal region [40–44]. DIE is rarely present only in the

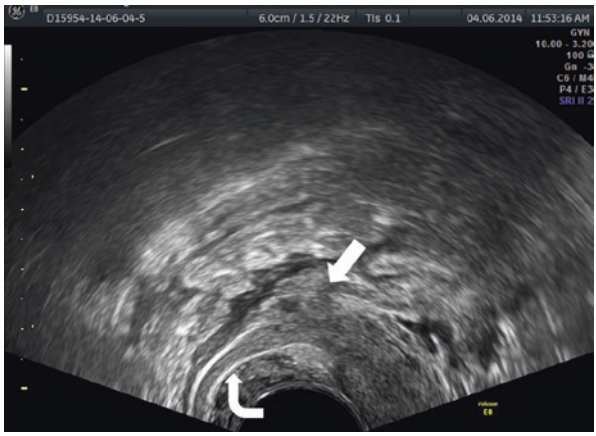

Fig. 16.15 An endometriotic nodule of rectovaginal septum at ultrasonography. The curved arrow indicates the normal vaginal wall

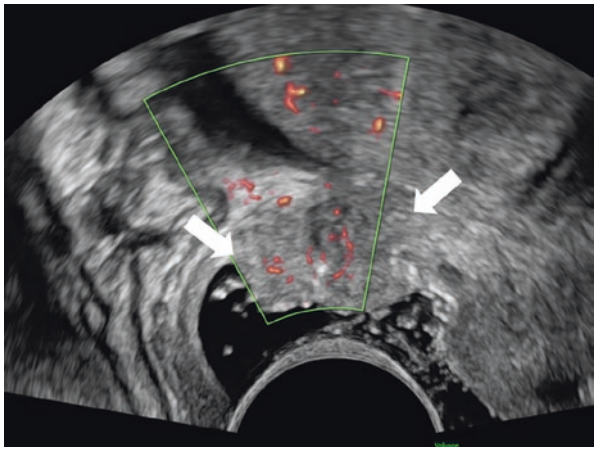

Fig. 16.16 An endometriotic vaginal/forniceal nodule at ultrasonography

rectovaginal septum (RSV), which includes vagina, rectum, and septum. DIE in RVS appears as a retroperitoneal nodule in the rectovaginal area under the lower posterior cervical wall [21, 40–44] (Fig. 16.15). The posterior vaginal wall/fornix DIE nodule is, generally, an avascular lesion, which appears isoechoic to the vaginal mucosa, and it extends into the vaginal cavity, becoming visible by speculum examination [21] (Fig. 16.16). In cases of DIE in rectum/rectosigmoid bowel, the operator using transvaginal ultrasonography should detect multifocal and/or multicentric lesions in the anterior rectum, rectosigmoid junction, and/or sigmoid colon. Their typical aspect is a hypoechoic thickening of the muscularis propria or a hypoechoic nodule, which can be associated with hyperechoic foci [40–44] (Fig. 16.17). The examiner can visualize uterosacral ligaments (USLs) lesions in the midsagittal retrouterine area, as hypoechoic thickening, which can involve nearby structures [40–44] (Fig. 16.18).

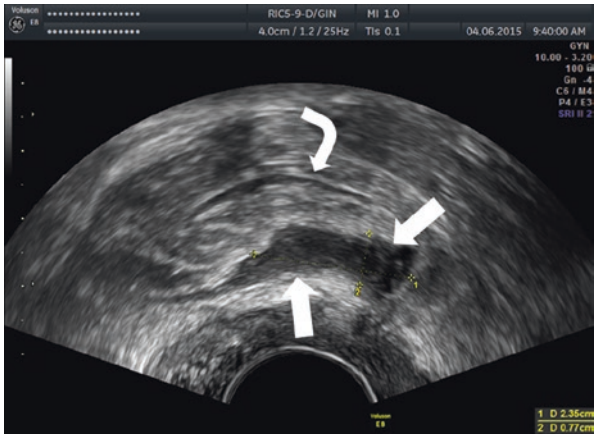

Fig. 16.17 A rectosigmoid nodule of endometriosis at ultrasonography (straight arrow) with the posterior wall of rectosigmoid (curved arrow)

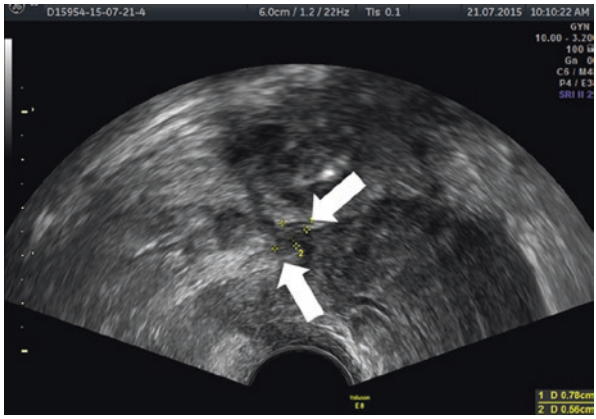

Fig. 16.18 A nodule of uterosacral ligament at ultrasonography

The overall diagnostic performance for DIE lesions in rectosigmoid localization is good, as demonstrated in recent meta-analysis, with high sensitivity (91%, with 95%CI, 85–94%) and high specificity (97%, with 95%CI, 95–98%) [45], and it was significantly higher than the overall diagnostic performance of TVS for assessing DIE in USLs, RVS, vaginal wall, and bladder [46]. Moreover, a recent meta-analysis has compared the diagnostic performance of TVS and MRI, respectively, concluding that it is similar to assess DIE lesions in rectosigmoid, USLs, and RVS [47].

In conclusion, imaging modalities can investigate accurately in adolescent and young adults the presence of an endometrioma, the association with POD occlusion, the rare but possible presence of DIE, and finally the presence of adenomyosis.

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Chapter 17
Utility of Ultrasound in the Evaluation of Adolescents Suspected of Endometriosis

Caterina Exacoustos, Francesco Giuseppe Martire, Lucia Lazzeri, and Errico Zupi

Introduction

The adolescent patient is often referred to the gynecologist for dysmenorrhea associated with nonspecific abdominal pain. Gastrointestinal symptoms, such as acute abdominal pain, severe constipation, diarrhea, and nausea, are other frequently reported symptoms. The presence of severe cyclic pain characterized by uterine cramping, abdominal pain, low back pain, and lower pelvic pain, combined with other symptoms (such as nausea, vomiting, anorexia, drowsiness, headache, vertigo, weakness, syncope), has a prevalence of 60–75% in all adolescent girls [1, 2]. Less frequently, ovulatory pain, dyspareunia, and excessive menstrual bleeding are symptoms at onset. The study of Yang et al. [3] showed that one-third of adolescent girls affected by endometriosis reported episodes of acute abdominal pain and gastrointestinal dysfunction. According to a review by Chapron et al. [4], the main warning signs of endometriosis in adolescents are prolonged intake of nonsteroidal anti-inflammatory drugs (NSAIDs), family history of endometriosis, more frequent absenteeism from school during menstruation, and prescription of COC before age 18 years because of severe primary dysmenorrhea. In 10% of cases, dysmenorrhea is secondary to other diseases such as congenital Müllerian anomalies, ovarian cysts, pelvic inflammatory disease, and adhesions [1].

Zannoni et al. [7] recently conducted a study on 250 adolescent girls referred to family counseling services for different indications and showed that 12% of adolescents presented symptoms suggestive of endometriosis. Although the presence of

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classic symptoms and the use of sonography help to formulate the diagnosis for the majority of diseases responsible for secondary dysmenorrhea, endometriosis is particularly problematic in adolescents and may be misdiagnosed even by the most meticulous gynecologists. Missing a prompt diagnosis means missing the opportunity to refer the adolescent to a specialty center, which could halt disease progression. Dun et al. found patients (n = 25) with a mean age of 17.2 had experienced symptoms for an average of 22.8 months and seen a median number of three physicians before receiving an accurate diagnosis [5]. Therefore, with adolescents, it is essential to examine all the possible aspects related to the suspicion of endometriosis; a review of past medical history and a review of symptoms should be actively conducted with systematic questions to the patient about symptoms and possible comorbidities suspicious for endometriosis. Also, the pelvic evaluation vaginal or transrectal [6] could add some information; the onset of pain at palpation of the vaginal fornices and the rectovaginal septum or at mobilization of the cervix, the detection of palpable nodules in the vaginal fornices or in the paracervical regions, the deviation of the cervix from the midline, and the presence of blue lesions on the surface of the cervix should all be considered as useful clinical findings for making the diagnosis of endometriosis. Moreover, it should be specified that the sensitivity of the clinical examination is greater when the examination is performed during the premenstrual period.

Finally, imaging by pelvic ultrasound and/or magnetic resonance investigation (MRI) may be valuable in the diagnosis. However, as most affected adolescents are at stage I or II of the disease with shallow tissue invasion, pelvic examinations such as ultrasound and MRI probably do not contribute greatly to the detection of endometriotic disease in teenagers [8, 9].

Ultrasound in Adolescents with Suspected Endometriosis

Ultrasound Approaches

The transabdominal approach permits a nonspecific evaluation of the pelvis, and its diagnostic accuracy in detecting endometriotic lesions is mainly related to the presence of ovarian endometriomas, uterine anomalies, and bladder lesions. Transabdominal ultrasound (TAUS) of the pelvis is usually best performed with a curved transducer and is most effective if the patient has a full bladder. The full bladder provides an acoustic window, displaces the bowel away from the area of interest, and orients the uterus in a position that is perpendicular to the sound beam, an orientation that affords better axial resolution and an improved image. There are limitations to TAUS, especially overlying bowel gas, and patient's body habitus can confound transabdominal imaging. The lower-frequency transducers, necessary of better tissue penetration, suffer from lower resolution and resulting lower image quality (Fig. 17.1).

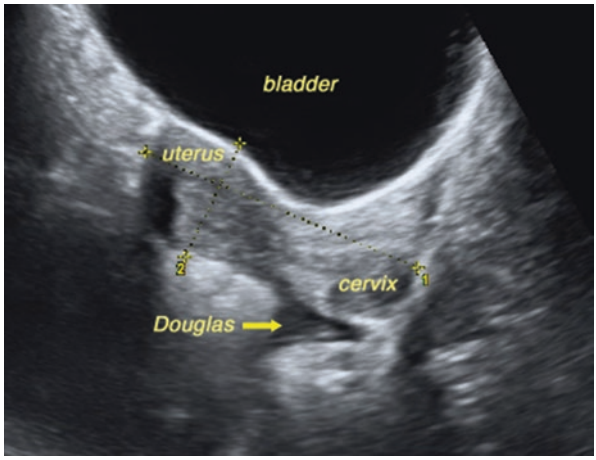

Fig. 17.1 Transabdominal ultrasound appearance of the uterus in a young girl with dysmenorrhea. Note the ill-defined pouch of Douglas where fluid and probably some adhesion could be seen

Transvaginal sonography (TVS), which is the first-line imaging modality in gynecology, allows the evaluation of volume, shape, and content of the uterus, both ovaries, rectum, and bladder, with good diagnostic accuracy for endometriotic lesions. The primary advantage of TVS over TAUS lies in the ability to place a high-frequency transducer next to the region of interest, without the intervening abdominal wall and other structures that can compromise abdominal ultrasound imaging. This allows optimal visualization of the uterine corpus and cervix, the ovaries, adnexal regions, and cul-de-sac, as well the urinary bladder and rectum. TVS is particularly useful in the evaluation for imaging the retroverted uterus and retrocervical region. Furthermore, it can be useful in diagnosing of myometrial alterations such as adenomyosis and, if performed by expert sonographers, can detect pelvic floor and rectovaginal lesions. Performing the sonography with the vaginal probe can also be associated with indirect signs of the disease, the so-called soft markers (painful trigger points with pressure with the vaginal probe, the presence or absence of mobilization of the ovaries, the presence of fluid in the pelvis), to increase the diagnostic sensitivity of the examination [10, 11]. The major limitations of TVS are virginal patients, the inability to evaluate the external uterine contour adequately, and the lack of global view of pelvis.

The vaginal transducer can also be used transrectally, a technique that is very useful for the evaluation of virginal patients or those with congenital vaginal hypoplasia or agenesis. The probe is inserted into the rectum and advanced until a midline image of the cervix is visualized in a longitudinal scan (Fig. 17.2). The uterine cervix, parametria, vagina, and rectal walls are evaluated by moving the transducer along the main axis in both axial and longitudinal planes. A transrectal approach may be considered in *adolescents* with an intact hymen as it is essentially atraumatic if performed carefully and is similar to TVS in the imaging and diagnostic accuracy of endometriotic lesions of the pelvis.

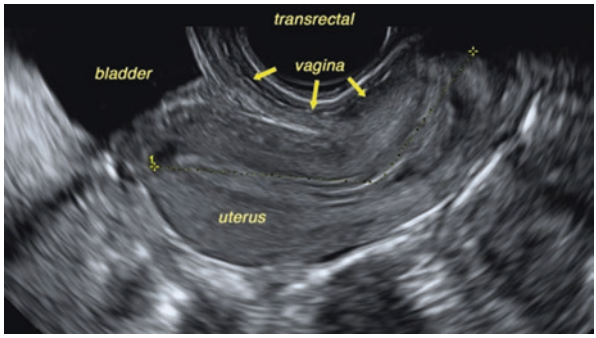

Fig. 17.2 Transrectal ultrasound with transvaginal probe. Appearance of a normal anteverted uterus. Note the view of the vaginal canal and the other pelvic organs, uterus and bladder, very similar to the transvaginal approach

Ultrasound Findings of Endometriosis in Adolescents

Pelvic endometriosis typically manifests as (1) superficial peritoneal lesions, (2) ovarian endometrioma, and/or (3) deep (or solid infiltrating) endometriosis (DIE), which is histologically defined as a lesion that extends more than 5 mm into the subperitoneal space and/or that affects the wall of pelvic organs and ligaments. Since most affected *adolescents* are at lower stage of the disease with small endometriotic lesions and superficial tissue invasion, ultrasound investigation does not often detect clearly endometriotic disease, and few indirect sonographic sign could help to perform the diagnosis.

Endometriomas

Transvaginal ultrasound is the principal technology for the image-based diagnosis of ovarian endometriomas. The "typical" endometrioma manifests as a unilocular cyst with ground glass echogenicity and no to moderate vascularization [12, 13]. The "atypical" endometrioma presents as a unilocular cyst with ground glass echogenicity and *papillary projections* (protrusion of solid tissue into the cyst lumen with a height of 3 mm or more) and no flow inside the papillary projection [12]. In fact, these are not a true papillations of solid tissue but images created by blood clot or fibrin lying adjacent to the cyst wall that assumes a regular surface and rounded shape. The pattern of endometriomas with complex echotexture, thick walls, and solid echogenic appearance of hemorrhagic clots within the endometrioid cystic cavity may be misinterpreted as mature teratomas, serous cysts, or hemorrhagic corpora lutea (Fig. 17.3).

In *adolescent*, small endometrioma less than 3 cm could be observed (Fig. 17.4). These small endometrioma could be fixed posteriorly to the uterus, in the pouch of Douglas, or to the homolateral uterosacral ligament. In case of bilateral endometriomas, both ovaries could be fixed posteriorly to the uterus and adherent to the contralateral ovary (kissing ovaries) (Figs. 17.5 and 17.6).

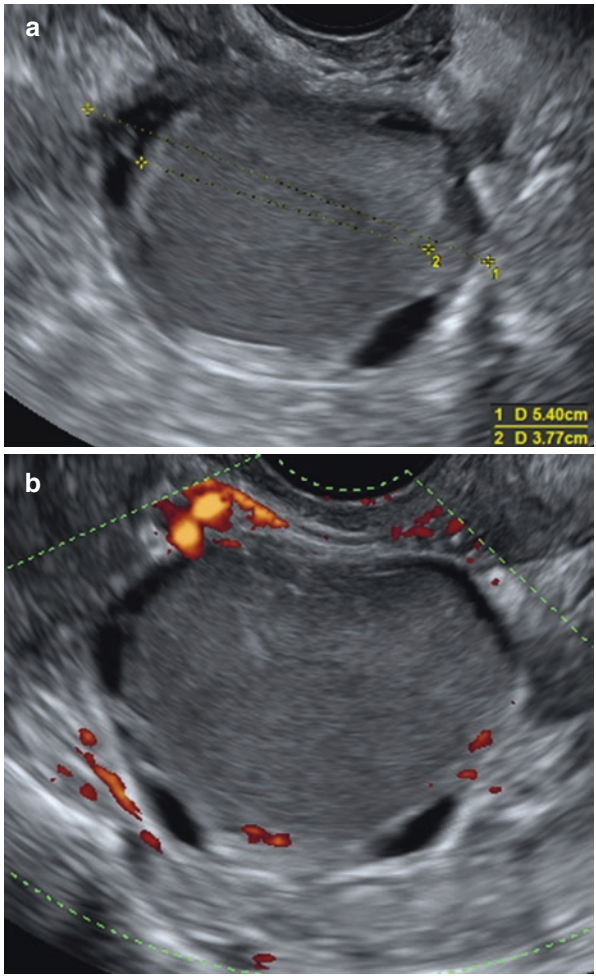

Fig. 17.3 Ultrasound appearance of a small ovarian endometrioma: a unilocular cyst with ground glass echogenicity (**a**) and few vascularization in the hyperechoic cyst wall (**b**)

Adhesions

Normally, uterus and ovaries are mobile and not adherent to the surrounding tissues by palpation with the probe and/or by abdominal palpation with the hand; these organ's movements could be seen at ultrasound (sliding sign) [11]. Adhesions can be suspected during the TVS examination if the ovaries and/or the uterus appeared fixed to the adjacent structures (broad ligament, POD, bladder, rectum, and parietal peritoneum) while the sonographer conducted an abdominal or vaginal palpation. The presence of pelvic fluid, fine septa, or strands of tissue (adhesions) between the ovary and uterus or the peritoneum of the pouch of Douglas (POD) [10, 14, 15] are associated to more filmy adhesions. The POD obliteration was assessed using the sliding sign by gently pressing on the cervix with the TVS probe or palpating the uterus abdominally with a hand to determine whether the rectosigmoid glides freely

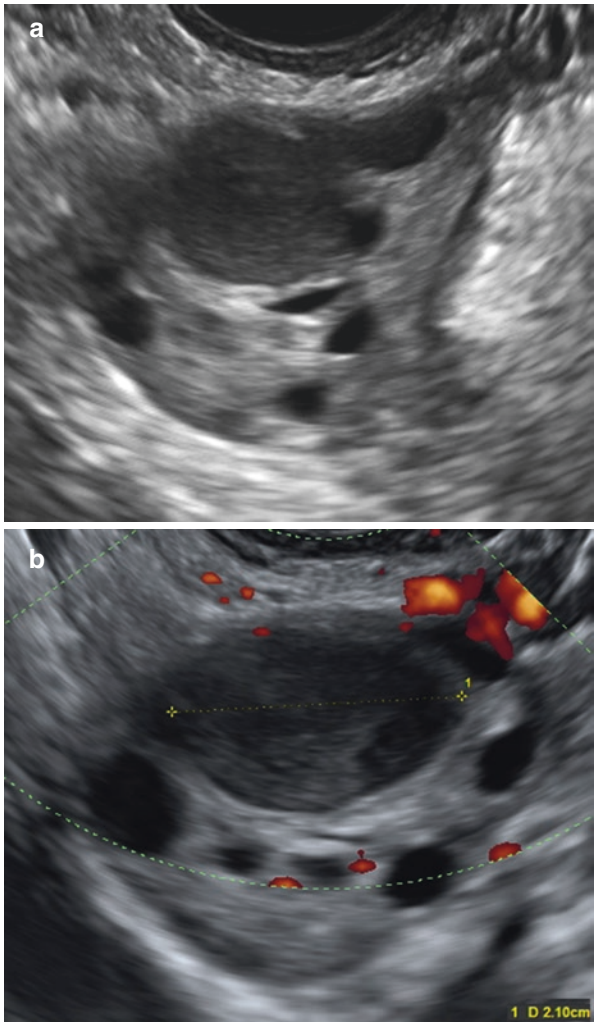

Fig. 17.4 (**a**, **b**) Transvaginal ultrasound appearance of a small ovarian endometrioma in a 16-year-old girl: (**a**) unilocular cyst with ground glass echogenicity and (**b**) no vascularization around the cyst. Note the normal multifollicular ovarian tissue around the cyst

over the posterior wall of the upper uterus/fundus [11, 16]. A negative sliding sign has a very high diagnostic efficiency for prediction of DIE of the rectum and pouch of Douglas obliteration [17, 18].

Endometriosis may cause adhesions especially in presence of superficial peritoneal lesions or small nodules in the pelvic organs, which are very difficult if not impossible to detect by imaging. Therefore, in *adolescent* patients with chronic pelvic pain, it is important to look for sonographic signs of adhesions. TVS "soft markers" (i.e., site-specific tenderness, reduced ovarian mobility) correlate with the presence or absence of endometriosis and adhesions at laparoscopy [10, 18]. When pressure is applied between the uterus and ovary, a combination of three features is suggestive of ovarian adhesions and fixation of the ovaries to the uterus: blurring of the ovarian margin, the inability to mobilize the ovary on palpation (fixation), and

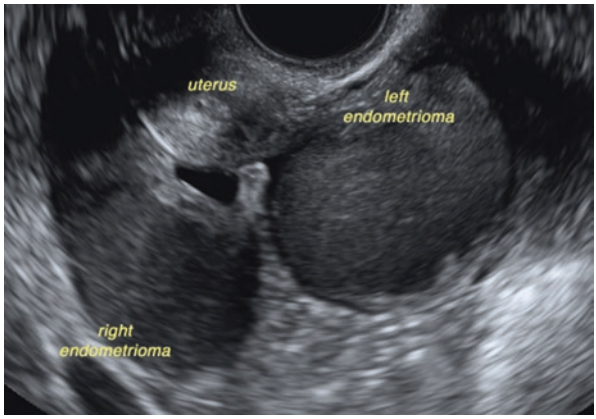

Fig. 17.5 Ultrasound image of bilateral endometriomas with both ovaries adherent to each other (*kissing ovaries*) and posterior to the uterus

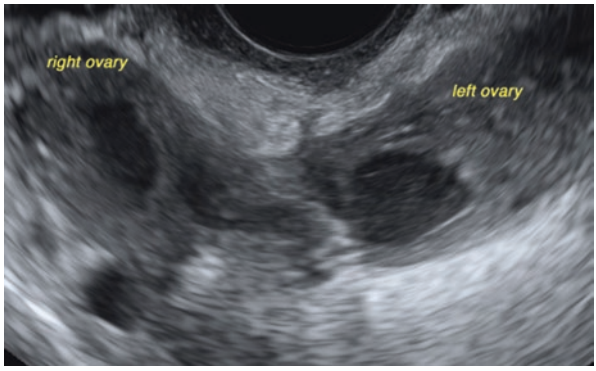

Fig. 17.6 Ultrasound image of the two ovaries adherent to each other (*kissing ovaries*) both with a very small endometrioma

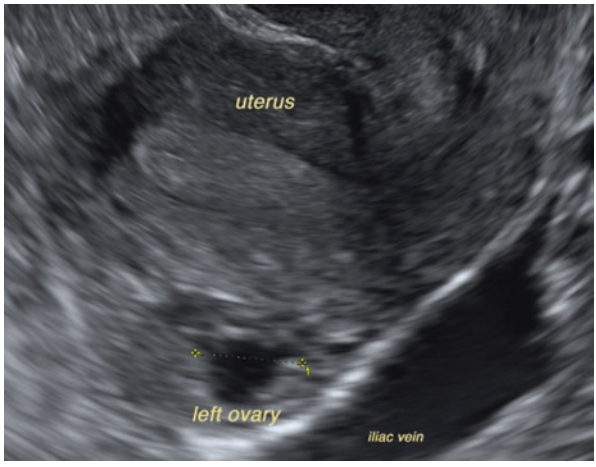

Fig. 17.7 Ultrasound appearance of an ovary attached posteriorly to the uterus seen in longitudinal section due to adhesion between these two organs; sliding sign was negative

an increased distance from the probe [19, 20] (Fig. 17.7). Transvaginal and transrectal ultrasound have also been used to predict rAFS stages 3 and 4 endometriosis including pelvic adhesions [14, 15].

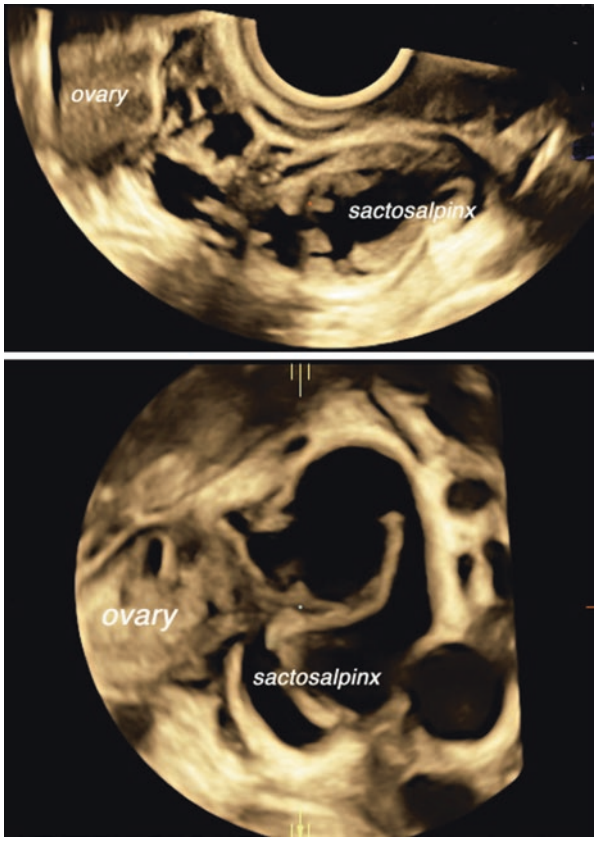

Fig. 17.8 3D ultrasound multiplanar view of a hydrosalpinx. Note the dilated Fallopian tube with fluid content. Small hyperechoic mural papillations are seen on the longitudinal section (**a**). Thin walls, incomplete septa, and the typical retort-shaped tubular structure are seen on the coronal section (**b**)

Rarely in *adolescent* patients, pelvic endometriosis involved salpinges mostly in terms of adhesions that altered the normal tubal course and occluding the tube, rarely by DIE foci affecting the tubal walls. Sactosalpinx can be observed near the endometriotic adhesions or lesions. In case of endometriosis of salpinx, a typical aspect of dilated Fallopian tube with thick walls and incomplete septa is visible (Fig. 17.8) with a fluid dense content similar to this of endometrioma (hematosalpinx) [21]. In case of occlusion of the tube due to adhesion or DIE that involved the distal part and the fimbriae, a hydrosalpinx is seen with the typical "beads-on-a-string" sign, defined as hyperechoic mural nodules measuring about 2–3 mm and seen on the cross section of the fluid-filled distended structure [21]. It seems very important in case of endometrioma or DIE to look by ultrasound carefully at tubal status.

Deep Infiltrating Endometriosis (DIE)

Imaging of *adolescents* with suspected DIE includes details of the anatomic localization, the size and number of lesions, the depth of infiltration of the nodules, and the degree of bowel involvement. A systematic evaluation of urinary tract in patients

with suspected DIE is also recommended because the prevalence of endometriotic lesions in urinary tract may be underestimated [22, 23].

TVS or transrectal sonography with vaginal probe is also, in *adolescent* girls, the first-line imaging technique when DIE is suspected. MRI is employed as a second line of investigation performed in selected patients according to the outcome of TVS and the severity of symptoms. Transabdominal sonography has not sufficient resolution for an accurate detection of DIE, and therefore, to evaluate virginal *adolescent* for suspected DIE, transrectal ultrasound is needed.

Adolescent patients with suspected DIE should undergo a detailed systematic examination of the pelvis to evaluate the anatomy of the uterus and the adnexa, both in the sagittal and horizontal plane, with gentle probe movements to assess for the presence of adhesions. A careful evaluation of all the painful sites is evoked by a gentle pressure of the probe ("tenderness-guided" ultrasonography) [24]. TVS examination is based on a detailed evaluation of organ and tissues dividing the pelvis in anterior, lateral, and posterior compartment [25–27].

DIE of Anterior Compartment (Bladder)

Adolescent patients are invited not to empty completely the bladder before TVS scan. The slightly filled bladder permits to better evaluate the structure of the walls and the presence of endometriotic nodules. Bladder adhesions of the vesicouterine pouch are evaluated by the presence or absence of the "sliding sign" between the uterus and bladder. Bladder endometriosis is considered only in case of infiltration of the bladder wall and not in case of adhesions or superficial peritoneal implants on the bladder serosa.

In *adolescent*, bladder nodules are very rare and generally small, and they appear as hypo- or hyperechoic linear or spherical thickening of the bladder wall, with or without cystic areas and regular/irregular margins, and bulging toward the lumen, involving mostly only the muscularis and serosa (Fig. 17.9).

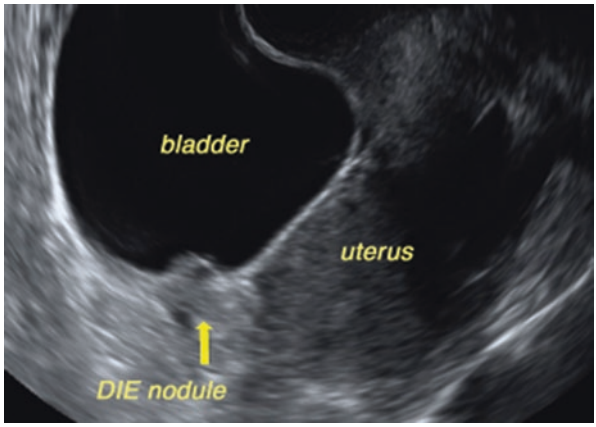

Fig. 17.9 Ultrasound image of an endometriotic bladder nodule (yellow arrow). The slightly filled bladder makes it possible to see the irregular margins of the hyperechoic lesion bulging into the lumen of the bladder and infiltrating the bladder dome wall. The nodule is not attached to the uterine anterior wall

In the assessment the DIE position in the bladder, the vescical organ can be divided into three zones: 1. the trigon zone and vescical base, 2. the vescical dome (which lies superior to the trigone and is intra-abdominal), and 3. the anterior retroperitoneal wall [23, 27]. The trigone is seen by TVS as a thickening of the bladder wall within 3 cm of the urethral opening, delimited by the two ureteral orifices laterally. Bladder endometriosis in *adolescent* patients is located more often on the vesical dome or the level of the Retzius space (Fig. 17.9). The dimensions of the nodule should be recorded, as well as the distance between the nodule and the ureters and the trigone [23, 27].

DIE of Lateral Compartment

Special attention must be paid to the parametrium and to the pelvic ureteral evaluation and in particularly in the paracervical area. In adolescent patients, parametrial DIE is rare and very small in size but can cause some uterine lateral deviation. Therefore, parametria should be carefully examined lateral to the uterine cervix firstly on the sagittal planes, moving the probe from the lateral sites where the parametrium is attached to the cervix, to the uterine vessels bifurcation, to the lateral pelvic wall, and then on the transverse planes, moving the probe from the uterine isthmus to the external cervical os. The parametrial involvement in adolescent is rarely seen as an infiltrating hypoechogenic irregular fibrotic endometriotic tissue, but it can also be suspected when the uterus is fixed laterally or if there is a lateral rotation of the uterus due to a retraction of the parametrium or uterosacral ligament by fibrotic endometriotic tissue.

Pelvic ureteral dilatation can be easily seen by TVS as a tubular anechoic image with or without movements in the parametrial tissue, very similar to a blood vessel but with negative color/power Doppler signs. In case of extrinsic compression without stenosis of the ureter, the TVS diagnosis is more difficult. The distal part of the ureter can be identified adjacent to the bladder trigon and followed laterally to the cervix, to the pelvic brim, and to the level where it crosses the common iliac vessels [28]. An extrinsic compression also without ureteral dilatation could be suspect in case when a DIE lesion is located close to the ureter. The hypothesis of a ureteral involvement suggests a specific and accurate evaluation at the time of surgery and, in these cases, transabdominal ultrasound to evaluate the renal pelvis.

DIE of Posterior Compartment

DIE of the vagina is seen as a nodular thickening of the vaginal wall that does not get thinner with probe compression. The nodule may be hypoechoic, homogeneous, or inhomogeneous with or without cystic areas, and there may be also some vascularization at power Doppler more than in nodule in other site. More frequently, the lesions are localized in the posterior vaginal fornix, and due to the compression of the probe, they can be misdiagnosed especially in adolescents who show small vaginal

lesions or only retraction. Vaginal endometriosis is seen by transvaginal or transrectal sonography often only as a small thickening of the posterior vaginal wall is, the comparison to the wall thickness of other part of the vagina could be useful to better detect these small lesions of the posterior fornix. A better detection of posterior vaginal DIE can also be achieved by increasing the amount of ultrasonographic gel inside the probe's cover for better visualization of the vaginal walls and posterior and anterior fornix [29] (Fig. 17.10).

DIE of the rectovaginal space RVS is seen as a hypoechoic lesion replacing the normal hyperechoic aspect of this layer between the vagina and the rectum. It seems very important to evaluate in *adolescent* patients small lesion below the peritoneum between the vagina and rectum which are not seen by the diagnostic laparoscopy which is often be performed in this patients when imaging is negative. Generally, RVS DIE has been described as endometriotic lesions that primarily infiltrate the RVS with probably extension in the rectum and/or in the posterior vaginal fornix.

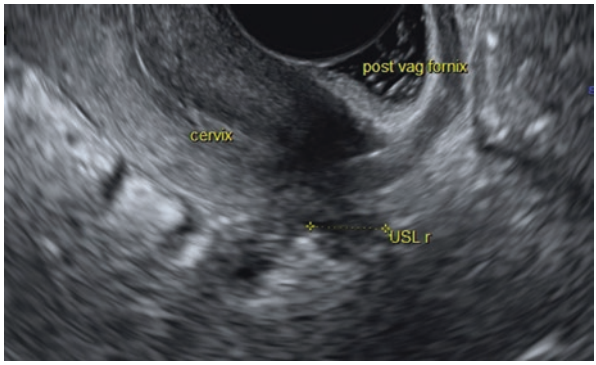

Fig. 17.10 Visualization of the posterior vaginal fornix filled with gel; note the wall of the vaginal posterior fornix, the cervix, the rectovaginal septum, and the retrocervical nodule of deep infiltrating endometriosis (DIE) infiltrating the right uterosacral ligament (yellow dot line)

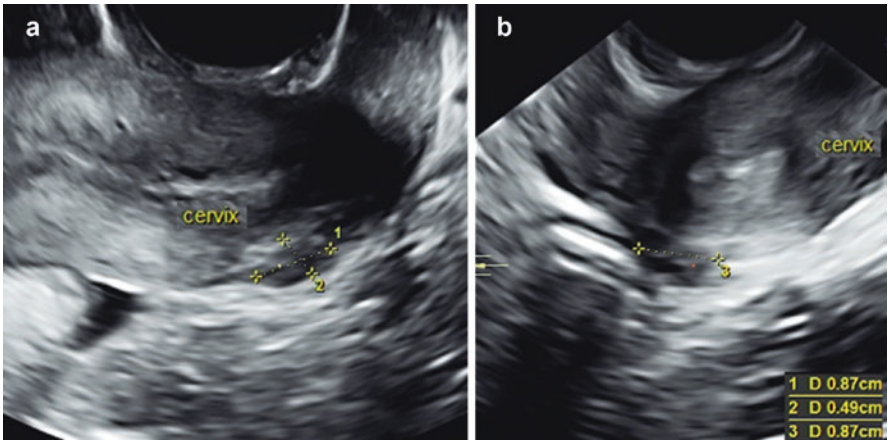

Fig. 17.11 (**a**, **b**) Ultrasound appearance of a small DIE lesion of the right uterosacral ligament which appears hypoechoic due to the infiltration and thickening caused by the fibrosis induced by DIE. (**a**) Longitudinal and (**b**) transverse sections of the cervix

Uterosacral ligaments (USL) DIE lesions can be seen in the longitudinal view of the uterus at their insertion on the posterior lateral cervix wall as a nodule with regular or stellate margins or like a hypoechoic linear thickening (Fig. 17.11). On the transverse cervical section, these hypoechoic nodules appear on the posterior lateral part of the cervix and interrupt the hyperechoic external cervical fascia (Figs. 17.10 and 17.12). The ULS DIE is best seen by placing the transvaginal probe in the posterior vaginal fornix in the midline in the sagittal plane and then sweeping the probe laterally to the cervix (Figs. 17.10, 17.11, and 17.12).

USLs lesion may be isolated or may be part of a larger nodule extending into the vagina or into other surrounding structures (Fig. 17.13). In *adolescent* patients, this endometriotic thickness of RSV and USL is generally very small and difficult to detect, and the tenderness-guided TVS can help identify this small DIE nodules. It is important to measure these small nodules in order to evaluate the growth and

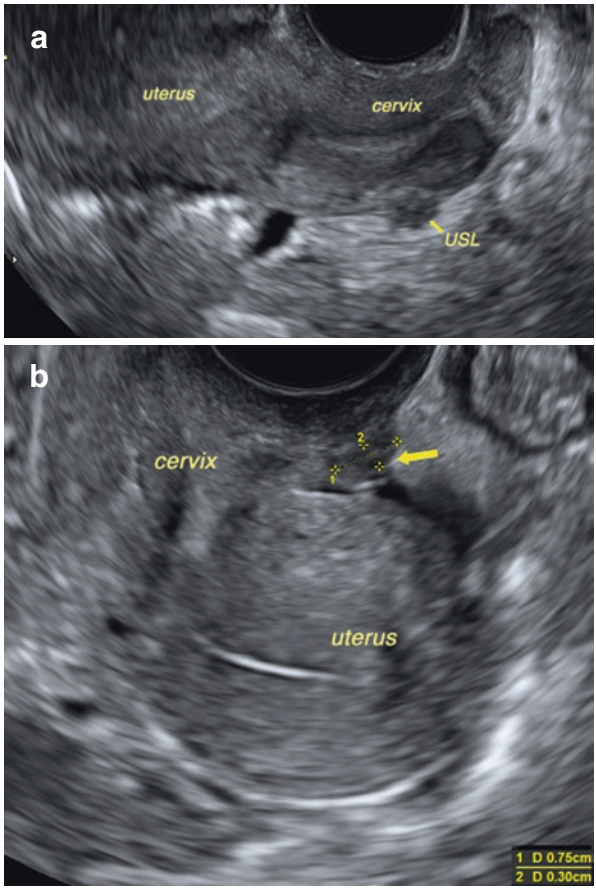

Fig. 17.12 TVS appearance of a small nodule of deep infiltrating endometriosis of the uterosacral ligament (USL) in teenager. (**a**) Note the small retrocervical DIE lesion (yellow arrow) in an anteverted uterus; (**b**) a similar USL node in a retroverted uterus (yellow arrow)

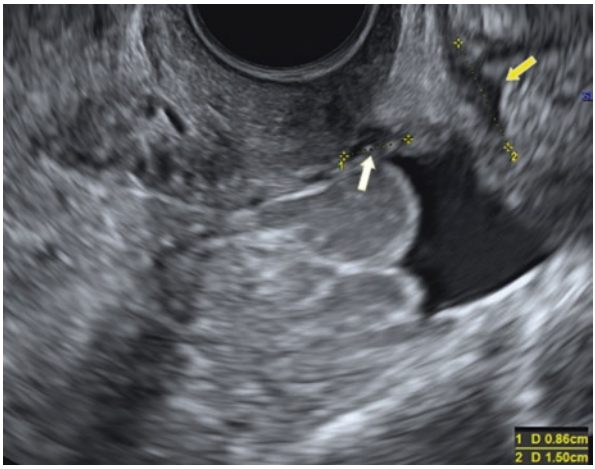

Fig. 17.13 Transvaginal ultrasound appearance of two small nodule of deep infiltrating endometriosis, one in the left uterosacral ligament (white arrow) and one small nodule infiltrating the rectal wall (yellow arrow). Note that both small nodules are under the peritoneum of the Douglas with fluid. Ultrasound appearance of different nodules of deep infiltrating endometriosis of the rectal wall. Since the lesion is located on different planes (yellow lines), the curved cutting of the nodule volume permits to evaluate better the size and extension of the lesion

modification during follow-up of these young patients. In some cases, the DIE lesion involving the USL is located at the torus uterinum. If so, it is seen as a central thickening of the retrocervical area between both USLs [25–27].

The rectum and the rectosigmoid segment are the most frequent site of bowel involvement also in adolescents, followed by the appendix, sigmoid colon, ileum, and cecum. At TVS, the normal rectal wall layers are seen: the rectal serosa and smooth muscle layer appear as a thin, hypoechogenic line covered by the rectal submucosa and mucosa which is visualized as a hyperechogenic rim covering the rectal smooth muscle layer [27]. DIE of the bowel appears also in adolescents as mostly small hypoechoic lesions, linear or nodular thickening of the bowel wall with irregular borders, and few vessels at power Doppler evaluation [25–27] (Fig. 17.14). The diameters of each lesion should be taken, also if often the irregular border did not permit accurate measurements. Volume acquisition with 3D TVS permits a more accurate measurement and evaluation of the DIE lesion in different planes. *In young patients*, the intestinal nodules are small and located below the peritoneum of the pouch of Douglas and are considered low rectal lesions (Figs. 17.15 and 17.16), and their detection not only by TVS but also during laparoscopy appears very difficult. Whereas the DIE lesions above the POD are considered upper rectal or the rectosigmoid junction lesions and are generally associated with adhesions with the uterus and left adnexa and retraction of the peritoneal tissues and therefore easier to detect by ultrasound and laparoscopy. Unfortunately in adolescents, the DIE nodules of the rectum are very small and mostly retroperitoneal, still without any evident sign of adhesions or logistic retraction (Figs. 17.15

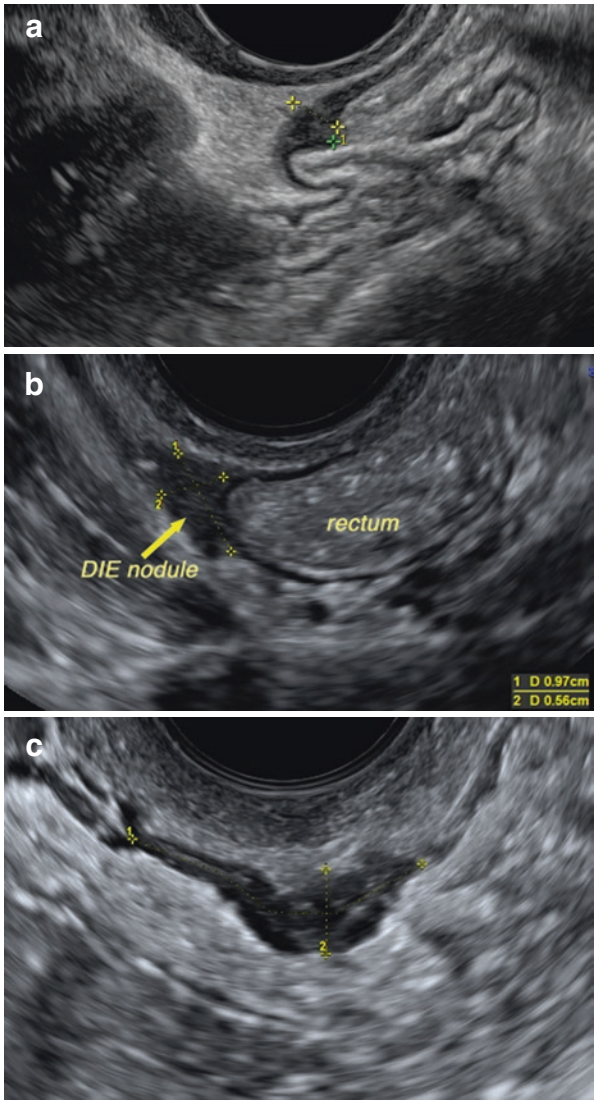

Fig. 17.14 Ultrasound appearance of three different nodules of deep infiltrating endometriosis of the rectum. Note the hypoechoic tissue infiltrating the muscular layer of the bowel. Note the different size and forms of the lesions. (**a**, **b**) Small lesions found in teenagers. (**c**) Larger lesion seen in a patient of 35 years. The curved cutting of the nodule volume permits to evaluate better the size and length of the lesion

and 17.16) and, therefore, often not detected by laparoscopy, but TVS can evaluate the retroperitoneal tissues and detect these small DIE nodules.

In the presence of a small DIE of the rectum, it is mandatory to look for other bowel lesion. Multifocal lesions are defined as the presence of deep lesions within 2 cm area of the main lesions or multiple endometriotic lesions affecting the same segment. Multicentric are defined as a satellite deep nodule found more than 2 cm from the main lesions or endometriotic lesions affecting several digestive segments [30]. TVS can clearly see the bowel wall until the rectosigmoid junction and,

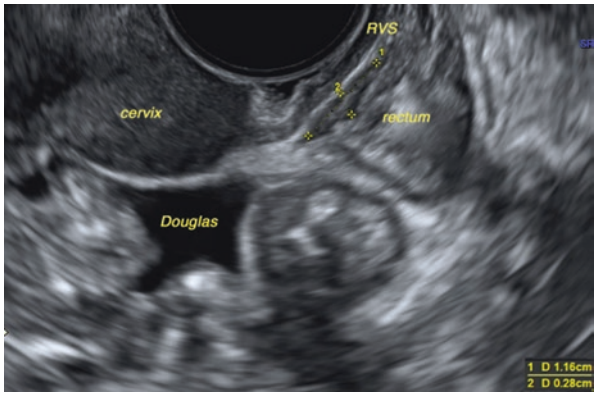

Fig. 17.15 Small nodule to the rectovaginal septum (yellow dot lines). Note that small lesion is completely under the peritoneum of the Douglas with fluid and can be easily missed by a laparoscopy

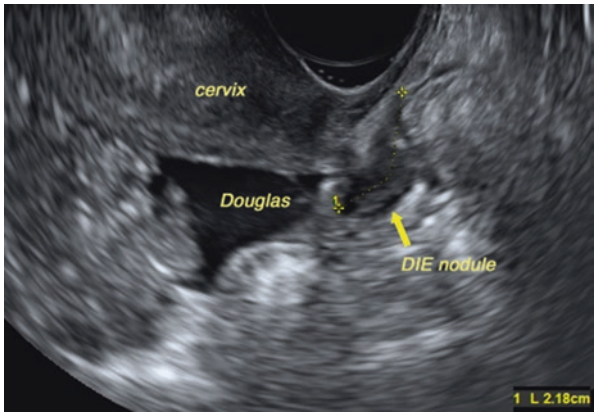

Fig. 17.16 Small nodule to the low rectal wall (yellow dot line). Note that the nodule is completely under the peritoneum of the Douglas with fluid and can be easily missed by a laparoscopy

therefore, to evaluate other bowel segments, MRI or CT is necessary, especially in young patients to exclude location at the appendix.

Adenomyosis

Adenomyosis is a common gynecologic disease characterized by the migration of endometrial glands and stroma from the basal layer of endometrium into the myometrium and is associated with smooth muscle hyperplasia leading, at ultrasound, to ill-defined lesions within the myometrium. Adenomyosis can be regarded as a disease of the junctional zone (JZ), where the endomyometrial barrier is impaired allowing infiltration of endometrial tissue into the myometrium [31]. Adenomyosis is a heterogeneous disease that may present in different phenotypes in the myometrium: diffuse, focal, and adenomyoma. Furthermore, the junctional zone (JZ) could be impaired allowing infiltration of endometrial tissue into the myometrium [31].

Contrary to the case with endometriosis, and despite the availability of noninvasive diagnostic tools, to this day, information on adenomyosis in *adolescent* girls

remains limited. In fact, the detection methods for adenomyosis remain a diagnostic challenge. TVS, along with MRI, has been shown to have high levels of accuracy in the diagnosis of adenomyosis [32]. Transvaginal ultrasound compared to MRI is better tolerated by young patients, reproducible, repeatable, less expensive, and widely available. Several studies have illustrated that the sensitivity and specificity of 2D (two dimensional) TVS in diagnosing adenomyosis are comparable to those of MRI and/or histology ranging from 75% to 88% and 67% to 93%, respectively [32–37]. However, all these studies regarding imaging and histopathological correlation have been done on hysterectomies mostly performed in patients over 40 years and, actually, there is few information on the correlation of adenomyosis ultrasound findings to histological in *adolescent*. The possibility to perform an atraumatic biopsy on the myometrium has been proposed by hysteroscopy [38].

2D TVS Features of Adenomyosis

According to several studies, the following 2D transvaginal sonographic features were considered to be associated with adenomyosis and defined as follows [32, 33, 35, 39–41]:

1. Globally enlarged uterus: The fundus of the uterus appears enlarged

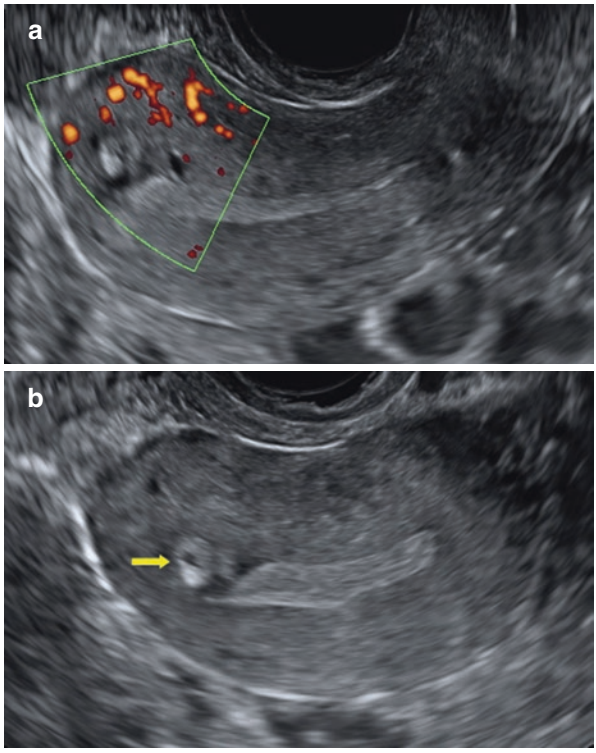

Fig. 17.17 Ultrasound image of a uterus with focal adenomyosis of the anterior wall. Note the round cystic anechoic areas in the inner myometrium or junctional zone. (**a**) Longitudinal uterine view with power Doppler. Note the translesional vessels. (**b**) Transverse uterine view of the same lesion. Note the small intramyometrial cysts surrounded by hyperechoic ring (yellow arrows)

2. Asymmetrically enlarged uterus (one uterine wall thicker than others) unrelated to leiomyoma
3. Round cystic area within the myometrium surrounded by a hyperechoic halo (Fig. 17.17)
4. Inhomogeneous, irregular myometrial echotexture in an indistinctly defined myometrial area with decreased or increased echogenicity; hyperechogenic islands, subendometrial lines, and buds.
5. Myometrial hypoechoic linear striations seen as a radiating pattern of thin acoustic shadows not arising from echogenic foci or leiomyoma (fan-shaped shadowing)
6. Indistinct, fuzzy endometrial-myometrial border (ill-defined endometrial stripe)
7. Presence of diffuse minimal vascularity seen as diffusely spread of small vessels which have not the normal course of the arcuate and radial arteries inside the myometrium
8. Question mark sign [42] defined when the corpus uterus was flexed backward, the fundus of uteri was facing the posterior pelvic compartment, and the cervix was directed frontally toward the urinary bladder

The myometrial involvement of adenomyosis can be defined by three basic phenotypes [41, 43, 44]:

- Focal can be defined when the cystic or hyperechoic lesions are surrounded mostly by normal myometrium (Fig. 17.17).
- Diffuse adenomyosis is described as diffusely distributed endometrial glands and stroma throughout the myometrium.
- Adenomyomas are a subgroup of focal adenomyosis surrounded by hypertrophic myometrium.

There is often an unclear distinction and confusion between adenomyomas and focal adenomyosis. Compared to both localized and diffuse adenomyosis, adenomyomas are relatively uncommon [33, 45, 46]. A variant of adenomyosis that seems specific to young women is the so-called myometrial cystic adenomyosis in which young patients present with nonresponsive severe dysmenorrhea [46]. 2D TVS has reached a high level of accuracy, and many authors have reported high agreement between ultrasound diagnosis of adenomyosis and histological findings. TVS should be the primary tool for the diagnosis of adenomyosis, with MRI being used when TVS is inconclusive [32].

Recent studies [43, 44] suggest also an evaluation of the amount of the disease inside the uterus with the hypothesis that small foci or a low-grade or mild disease could be more associated to young patients and more diffuse and severe disease in older, multiparous women.

In fact, the vast majority of cases of adenomyosis are reported in women aged between 40 and 50 years old [47]. However, age has not consistently been shown to be associated with the disease, and more recent studies evaluating age showed the presence of adenomyosis in young nulliparous women [48]. Presence of ultrasound

features of adenomyosis in young patients has been observed in 20–22% of cases [48]. The presence of at least one of the typical TVS features of adenomyosis creates actually, especially in young women, some concerns.

Adenomyosis also seems to be associated with endometriosis [31, 47, 49, 50]. A strong association between adenomyosis diagnosed by TVS and endometriosis, with 48–50% incidence of adenomyosis in patients affected by DIE, was found [49, 50]. Therefore, in the presence of endometrioma or DIE, an accurate evaluation of the myometrium should be performed to identify ultrasound features of adenomyosis. In adolescents, the value of knowing the presence of adenomyosis is in evaluating how many of the girls are likely to have adenomyosis contributing to their pain symptoms as well as any other form of pelvic endometriosis.

3D TVS Features of Adenomyosis

Although the junctional zone (JZ) can be visualized on 2D ultrasound, acquisition of a 3D volume enables a more complete assessment in the sagittal, transverse, and coronal plane as shown in a standardized multiplanar view [41, 51, 52]. 3D transvaginal sonographic signs of adenomyosis are based on the evaluation of the junctional zone on the acquired volume of the uterus in order to obtain the coronal view. On the coronal view, the junctional zone appears as hypoechoic zone around the endometrium, and it can be seen clearer in all planes of the multiplanar view [41, 51, 52].

The JZ may be regular, irregular, interrupted, not visible, and not assessable or may manifest more than one feature (e.g., irregular and interrupted). Any irregularity in the JZ can be described (e.g., cystic areas, hyperechogenic dots, hyperechogenic buds and lines) in each location in the uterus (anterior, posterior, lateral left, lateral right, fundus) [41, 51, 52] (Fig. 17.18). In order to avoid only subjective morphological evaluation of the junctional zone as irregularity and infiltration, objective parameters such as the measurement of the thickness of the junctional zone that radiologist generally uses on MRI have been proposed also for 3D junctional zone assessment [25, 47, 51]. The JZ and the total myometrial wall thickness can be measured perpendicular to the endometrium on the same section through the uterus. The maximum thickness of the junctional zone (JZmax) is measured at the area where the JZ appears to be at its thickest.

Increased JZ thickness in young women is a new finding; a progressive increase in diameter of the posterior JZ starting from the third decade of life and markedly accelerated in women > 34 years old has been shown in previous studies using MRI [34, 35]. Also, the subjective evaluation of infiltration and disruption by endometrial tissue in the junctional zone is an accurate tool for the diagnosis of adenomyosis in *adolescent* [41, 51, 52]. Small adenomyotic cysts can be detected in younger patients in the JZ as also in the outer myometrium. Sonographic features suggestive of adenomyosis may develop earlier in reproductive life than previously thought and may occur in association with dysmenorrhea and abnormal uterine bleeding and in concomitance with endometriosis [48].

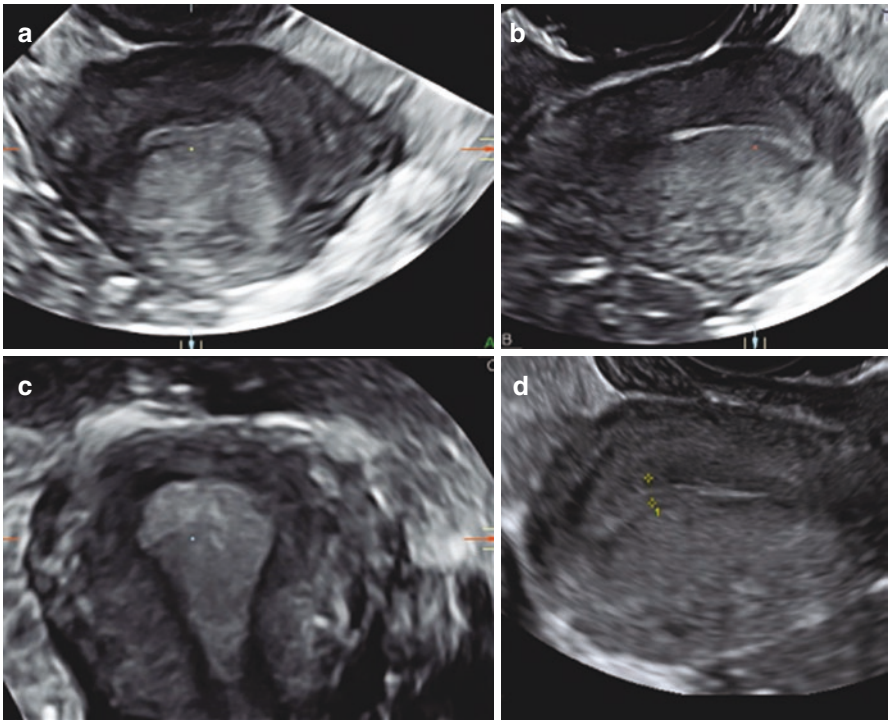

Fig. 17.18 *3D* multiplanar view of the uterus with adenomyosis of the outer myometrium in a teenager. Note on the transverse (**a**) and longitudinal (**b**) section the diffuse asymmetrical myometrial thickening with inhomogeneous myometrial echotexture and hyperechoic areas. On the coronal section (**c**), the junctional zone is regular. (**d**) 2D longitudinal view of the same uterus

Conclusions

In young patients, TVS showed great advantages over TAUS in the ability to place a high-frequency transducer next to the region of interest and to the possible endometriotic lesions in the pelvis. A transrectal approach with TVS probe may be considered in adolescents with an intact hymen.

In adolescent, endometriosis is present with small lesions and shallow tissue invasion, and therefore, ultrasound investigation if not performed very carefully does not contribute greatly to the detection of endometriotic disease in teenagers. However, if endometriomas are present also with small diameter, ultrasound is able to diagnose them accurately. This is not the case of DIE, which is not easily diagnosed, also because retroperitoneal lesions are in young patients very small. These small DIE lesions are often associated with pain symptoms, including chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and dyschezia, which can guide the ultrasound examination. The careful evaluation of diagnostic imaging findings gives

to the clinicians the opportunity to decide the best medical or surgical approach. In fact, TVS is able to see retroperitoneal DIE, which can be missed by a purely diagnostic laparoscopy.

2D TVS have reached a high level of accuracy in the diagnosis of adenomyosis, also in young patients. 3D ultrasound evaluation of the junctional zone and its alterations seems very important especially in adolescents with pain symptoms and suspect of pelvic endometriosis.

Although the sensitivity and specificity of TVS in the prediction of DIE and adenomyosis are high, their assessment by TVS is difficult and needs a great expertise. However, in adolescent patients, an accurate TVS can provide a lot of information, and being able to detect retroperitoneal endometriotic lesions and adenomyosis is probably better than a purely diagnostic laparoscopy that evaluates only superficial lesion.

Conflict of Interest All the authors report no conflict of interest.

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Part VII
Clinical Manifestations

Chapter 18
Neonatal Uterine Bleeding and Adolescent Endometriosis

Stephan Gordts, Sylvie Gordts, Patrick Puttemans, Rudi Campo, and Ivo Brosens

Introduction

Endometriosis defined as the extra-uterine localization of endometrial-like tissue affects 8–10% of women in the reproductive life [1]. The first publication mentioning the presence of endometriosis in the adolescent dated from 1946 [2]. The appreciation of the incidence of endometriosis in adolescent girls is frequently based upon the visual diagnosis by laparoscopy or histology. According to Yeung [3], the incidence of endometriosis is *estimated to be about one-third of adolescents with chronic pain, increasing up to 80% in adolescents with chronic pelvic pain who fail to respond to medical treatment.* Awareness of the presence of endometriosis in adolescents increased during the last decades. In a recent publication, staging of endometriosis according to the rAFS classification system reported an incidence of 3–92% stage I–II and 4–55% stage III–IV in adolescents with chronic pelvic pain [4]. Symptoms are dysmenorrhea frequently resistant to medication and cyclic or acyclic chronic pelvic pain, and recently a higher incidence of migraine was reported in these adolescents [5, 6]. Due to lack of awareness by the adolescents but even so by the professional healthcare providers, the delay between the first symptoms and the final diagnosis varies between 6 and 11 years [7]. Early onset of endometriosis is reported in a publication of the Mayo clinic reviewing young patients diagnosed with endometriosis in the period between 1935 and 1964; of the 68 diagnosed with endometriosis, 63 experienced menarche 5–10 years before complaining from dysmenorrhea and/or chronic pain [8]. Delayed diagnosis and treatment have significant consequences, as endometriosis is more advanced in women whose diagnostic laparoscopy is delayed, supporting progression of disease over time [9]. Nezhat et al. found patients ($n = 25$) with a mean age of 17.2 had experienced symptoms for

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an average of 22.8 months and seen a median number of 3 physicians before receiving an accurate diagnosis [6].

The pathogenesis up till now is a subject of an interesting discussion; Sampson's theory of the menstrual reflux is still the most widely accepted [10]. How to declare the presence of premenarchal endometriosis and the presence of severe endometriosis in adolescents still remains a fundamental question.

Premenarchal Endometriosis

The presence of endometriosis in five premenarchal girls, aged 8.5–13 years, and with chronic pelvic pain, has been described by Marsh and Laufer [11]. At laparoscopy he found the presence of clear and red peritoneal lesions. Alleviation of the pain occurred after treatment. Gogacz [12] described the presence of an ovarian endometrioma in an 11-year-old girl 6 months before the onset of menstruation. Clark [13], in 1948, described the presence of an endometriotic mass and uterus bicornis in an 11-year-old girl 8 months before the menarche, and Ebert [14] described the presence of histologic-proven endometriosis in a 9-year-old girl with chronic pelvic pain. It is obvious that endometriosis can be present in the premenarchal girl and in severe forms in the adolescent. Brosens et al. [15] suggested that the first retrograde menstruation occurs in the neonatal period and can be at the origin of early-onset endometriosis.

Neonatal Uterine Bleeding

Asking around midwifes and neonatal care units, the phenomenon is well known, but little or no attention is given to it. The English website WedMD [16] mentions the following: "Your Newborn Girl's Genitals and Bleeding": "Most dramatically, at 2 or 3 days of age, your daughter may have a little bit of bleeding from her vagina. This is perfectly normal -- it is caused by the withdrawal of the hormones she was exposed to in the womb. It will be her first and last menstrual period for another decade or so."

Recent research [17] looked for the literature related to the incidence of uterine bleeding in the neonate. Although no data could be found in the Anglo-Saxon literature, publications were present in French and German literature. Visible vaginal bleeding was reported to be present in 3.3–5.3% of the neonates, and incidence of occult bleeding, detected by cytology or biochemical tests, increased till 25.4–61.3% (Table 18.1). Neonatal menstruation occurs between days 3 and 7 postpartum. A large study on the occurrence of neonatal uterine bleeding was performed at the University of Novi Sad [18] on 2477 female newborns with 126 premature, 2241 at term, and 110 post-term. The incidence of NUB was, respectively, 0.78%, 3.79%, and 9.10%, indicating post-term neonatal menstruation is

Table 18.1 Reported incidence of neonatal uterine bleeding

NUB	Incidence	References
Visible	4.7%	Levy (1964) [19]
	5.3%	Kaiser and Grässel (1974) [35]
	3.3%	Huber (1976) [36]
Occult (Hb test)	61.3%	Kaiser and Grässel (1974) [35]
	25.4%	Huber (1976) [36]

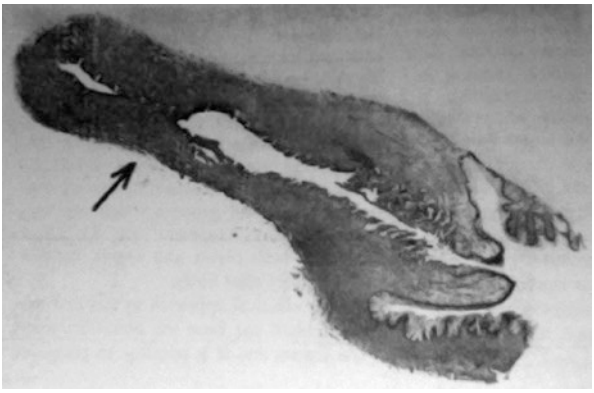

Fig. 18.1 Neonatal uterus: cervix is 2× longer than corpus (cervix right from arrow) (Fluhmann CF) [20]

very rare in preterm newborns but is increased in case of postmaturity (9.1%). A statistically significant difference was reported in the incidence of neonatal vaginal bleeding between preterm and post-term babies and between at-term and post-term babies, whereas there was no statistical difference between at-term and preterm babies [17]. An increased incidence was also noted in case of low birth weight, and the incidence of neonatal uterine bleeding in babies born to preeclamptic mothers was 42% (27/65) [19]. It seems that fetal hypoxia influences the occurrence of neonatal uterine bleeding. The main reason why neonatal uterine bleeding may be more likely to cause reflux of endometrial shedding is the difference in the uterine structure. A long cervical channel, twice as long as the corpus uteri, characterizes the neonatal uterus [20] (Fig. 18.1). Terruhn [21] described in his paper that, after the 26th week of gestation, injected liquid through the vagina does not enter the cervical channel anymore probably due to functional plugging of the endocervical canal by the secretory activity of its epithelium. It is therefore not unlikely that in case of endometrial shedding there is a higher possibility that desquamated endometrial cells are transported retrograde to the pelvis instead to become visible through a vaginal bleeding.

It is known that at the end of pregnancy fetal progesterone in blood is higher than the concentration of progesterone in the mother. Follicular growth is easy to identify from the 20th week of gestation [22], and the incidence of ovarian cysts in the female newborn amounts to 1 in 2500 [23]. As mentioned above, histologic examination of endometrial changes on autopsies of 169 newborns showed a proliferation in 68%, secretion in 25%, and decidualization in 5% [24].

The lack of any positive correlation between the changes seen in the ovaries and those seen in the endometrium leads to the inference that different endocrine stimuli and responses are involved and that the phenomena are unrelated. The findings of Lévy et al. [19] may suggest that obstetrical disorders involving preeclampsia, fetal growth restriction, or postmaturity may play a role in the accelerated endometrial maturation during intrauterine life.

In a case-control study involving 743 subjects, Borghese et al. [25] found patients with a birth weight of <2500 gr had a higher risk of endometriosis and that low birth weight is strongly associated with the risk of deep infiltrating endometriosis during adult life. Also Missmer [26] reported a correlation between lower birth weight and the incidence of endometriosis with a relative risk of 1.2 (95% CI 1.0–1.8, $p < 0.01$). It can be hypothesized that clinical conditions such as history of preeclampsia, low birth weight (<2500 g), and postmaturity are signs indirectly related to the development of endometriosis in adolescents. However it still remains unclear to which extent circumstances associated with neonatal menstrual-like bleeding can be used as a sign or symptom for suspecting endometriosis of neonatal origin.

It has been suggested that stem/progenitor cells are present in neonatal menstrual bleeding and may be linked to the early onset of endometriosis [27]. Neonatal stem/progenitor cells are able to survive in the absence of circulating estrogen levels and stay dormant for many years; it is postulated that with the onset of puberty these cells generate ectopic endometrial growth. Recent data looking for the presence of endometrial cells in peritoneal fluid in patients with and without endometriosis couldn't find any difference between the groups indicating that the presence of endometrial cells as such is not necessary for the development of endometriosis; this finding supports the importance of other mechanisms such as immunologic factors and endometrial stem cells [28].

Early Diagnosis

In daily clinical practice, the delay in diagnosis of endometriosis in the adolescent remains an important issue. Endometriosis in the adolescent is characterized by the presence of neoangiogenesis, red hemorrhagic peritoneal lesions, and, when more severe, ovarian endometrioma with adhesion formation. Already Hughesdon [29] described the presence of degenerative changes in the cortex underlying the cyst and in the underlying interstitial tissue. Kitajima et al. [30] demonstrated that in ovaries with endometriomas less than 4 cm in diameter, fibrosis is present, and follicular density is significantly lower than in cortex from contralateral normal ovaries. Smooth muscle metaplasia (SMM) is a common feature in ovarian endometriomas [31]. SMM and fibrosis are the result of repeated tissue injury, bleeding, and repair. Although in early stages of endometriosis in the absence of biomarkers progressivity cannot be predicted, progression of the disease has been reported. The longer the diagnosis was delayed, the more the endometriosis was in an advanced stage at the

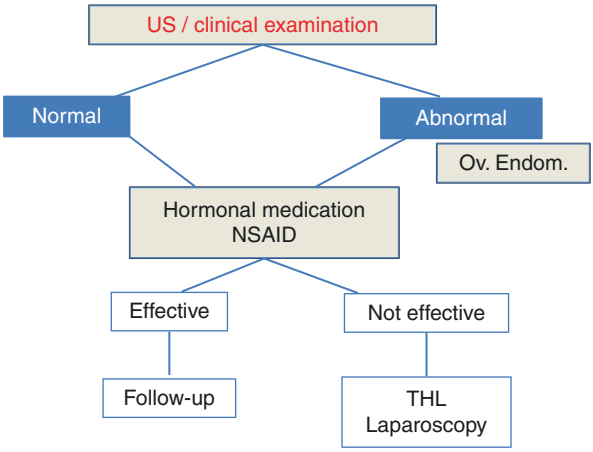

Fig. 18.2 Flowchart of adolescents with severe dysmenorrhea suspected for endometriosis. (Adapted from Gordts et al. [34]. Stepwise approach in diagnosis and treatment of adolescent endometriosis)

time of diagnostic laparoscopy [32]. Ultrasound is the first choice for diagnosing and monitoring early onset of uni- or bilateral endometrioma. Endoscopic exploration should be performed in the adolescent in case of severe dysmenorrhea not responding to medication, even with normal ultrasound findings, or when ultrasound monitoring shows an increase in the severity of the disease by the presence of ovarian endometriotic cyst increasing in size (Fig. 18.2). Although laparoscopy is traditionally recommended, the transvaginal laparoscopic exploration has been shown to be minimally invasive and safe in the early detection and treatment of ovarian and peritoneal endometriosis. In the absence of a contraindication for vaginal access, and when the ovarian endometrioma does not exceed 2 cm, the transvaginal laparoscopic approach allows an easy ablative surgery with minimal ovarian trauma [33, 34] (Fig. 18.3).

Conclusions

Neonatal uterine bleeding with retrograde reflux of endometrial cells could explain the presence of endometriosis in the premenarchal girl. It is still unclear if this NUB can be interpreted as a warning sign for the possible early development of endometriosis in the adolescent and adult women (Fig. 18.4). There are some tempting correlations between the higher incidence of NUB in case of fetal hypoxia and the finding of higher incidence of endometriosis in low-birth-weight infants and in case of preeclampsia. In the absence of a systematic recording of the NUB, it will be difficult to be drawn to a definitive conclusion. As most of the mothers and infants already left the hospital when NUB could occur, a close correlation with the mother and the pediatrician would be needed. It would be of interest if stem/progenitor cells could be identified in collected vaginal bleeding in the neonate. Albeit review the old literature on NUB and recent findings, it is unlikely that NUB can be seen as an insignificant clinical event.

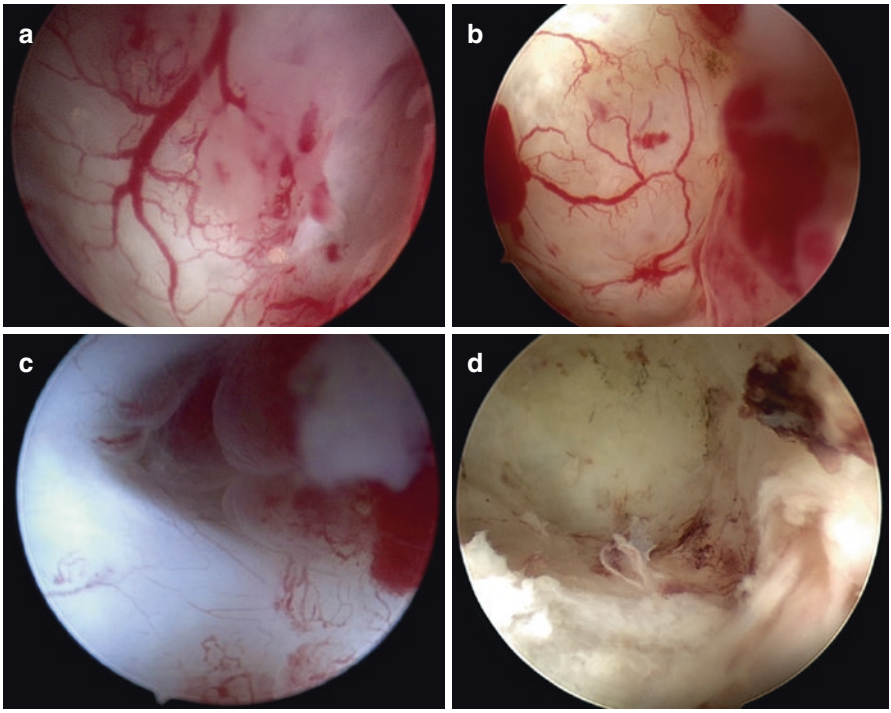

Fig. 18.3 (**a**–**c**) Insight view of small endometriotic cysts by transvaginal laparoscopy; remark the neoangiogenesis and presence of endometrial-like tissue; (**d**) result after ablative surgery using a 5-Fr bipolar probe

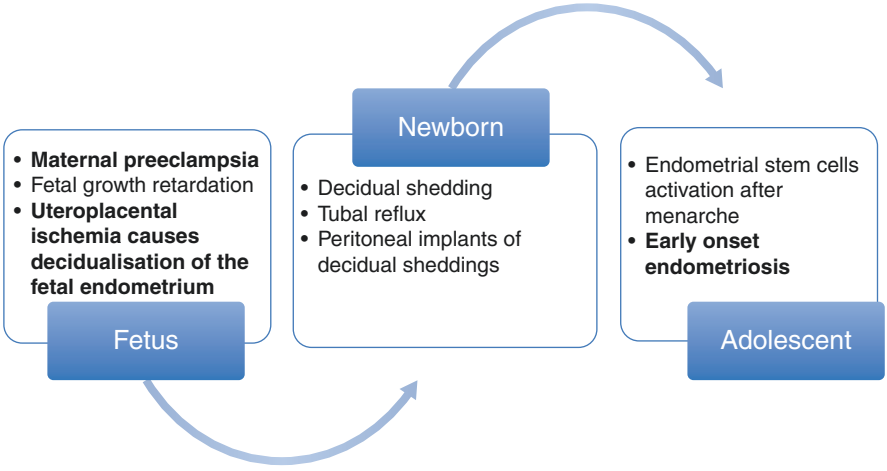

Fig. 18.4 Possible impact of NUB and fetal hypoxia on the development of premenarchal and adolescent endometriosis

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Chapter 19
Hammer and Nail Medicine: The Pervasive Ignorance of Endometrial Pain in Adolescents by the Mental Healthcare Profession

Minal Parekh Shah

The limits of my language means the limits of my world.

Ludwig Wittgenstein

Introduction

**Jerri* is a single woman in her 40s with emotional dysregulation severe enough to warrant a leave of absence from her job. Jerri relates a history of menarche at the age of 9 and remembers being doubled over by cramps to the point of inability to attend school. The incapacitating pain was generally accompanied by various degrees of spasms, pain, headaches, nausea, and vomiting. She was isolated when she was unable to engage in typical adolescent activities—dating, being with friends, and extracurriculars—due to the erratic nature of the symptoms and the irregularity of her cycle, as she never knew when the symptoms would begin once more. She was told month after month as a child "this is the burden we must bear…sweetie, we all suffer."*

Year after year, treatment was sought from a slew of psychiatrists, counselors, and psychologists—for the emotional fluctuations that seemingly came out of nowhere. Psychiatrists gave her antidepressants. Therapists engaged in cognitive therapy—attempting mind over matter. Friends were hard to come by as her large emotions made relationships unbearable for others. Her emotions left no room for forming connections and left her bereft of a significant relationship.

There was a normalization of the pathology by the culture of older women in her family which covertly and pervasively denied Jerri the identification of a potentially

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curative diagnosis. Psychiatry assumed the emotional instability to be the cause of her limited quality of life instead of being the symptom of a disease which diminished her quality of life. Because an occurrence of molestation which occurred at menarche, therapists targeted thoughts which were, in their opinion, caused by trauma leading to heightened emotionality. For *30 years*, she sought psychiatric/psychological help for the emotional lability that plagues her 3 out of 4 weeks each month—under a forced assumption that her cycle was regular. She has seen pediatricians, gynecologists, and internists—she always had access to the regularly expected medical care. That the emotional instability was a side effect of the symptom of behavioral maladaptation due to the pathology of a medical disease of endometriosis (or any illness for that matter) yet undiagnosed was not even a consideration by anyone she had crossed paths with—in 30+ years.

She was recently diagnosed with endometriosis due to a *psychotherapist's* recommendation for evaluation. It took a marginally medically trained therapist to ask about the relationship between her moods and behaviors to her monthly cycle leading to a realization that there was a high likelihood of endometriosis (and/or PCOS, PMDD, PID, or even the related IC), lending itself to a pattern of behaviors borne to cope with emotions of surviving her period over time. She stated that she has "one good week a month."

Upon intake, we asked "How old were you when you got your period?", "Describe your emotions each week of the month in a typical cycle.", and "Does the havoc you wreak during the 10 days before your period each month take you the other 20 days to recover?". The answers led to a referral to a reproductive endocrinologist. She was diagnosed with endometriosis, fibroids, and PMDD finally, in her 40s.

For Jerri, the focus of psychotherapy has shifted from learning coping skills for withstanding the dysregulation of emotions behaviorally to resolving the actual cause of the emotional dysregulation and the ensuing behavioral patterns that have evolved over 30 years to cope with maladaptive emotional urges brought on by hormonal fluctuations and the pain of endometriosis.

It is indeed heartbreaking to hear women say that their period is a "crime scene in my pants" or receive a call from the emergency room asking and pleading for someone to convince their attending physician that they are not "some junkie" and that they indeed need medication. When a cancer patient suffers pain, headaches, and nausea they are medicated and not told their moods are the result of untreated trauma. Nor are they told "you're a cancer patient…it's your burden to bear." Here, though pain is an expected, dare we say a "normal," phenomenon for chemotherapy patients, it is still recognized as suffering that must be alleviated, and all efforts are made to relieve the distress. When a migraine patient sees a neurologist, they are afforded access to pain medications, treatments (Botox, etc.), and triptans to reduce the frequency and severity of the suffering; even controlled medications are given, generally without doubting the patient's account even though migraine is an illness that is not detectable through laboratory testing.

This is not true involving disorders of the female reproductive system and especially not with adolescents and young women suffering from having to endure a sub-standard quality of life. In psychiatry and psychology, there are many factors that contribute to the marginalization of patients' suffering from physical disease and disorder when the manifestations are primarily emotional or behavioral in presentation. The emotional distress from the maladaptive behavioral coping mechanisms of physical disease is in the limelight without even an acknowledgement, much less inquiry into the shadow cast by physical disease.

The benefits of traditional counseling with an emphasis on exploration of the psyche and even the latest in Dialectical Behavior Therapy (DBT)[A] focusing on acute behavioral change are limited by a multitude of factors which delay the identification and treatment of endometriosis in adolescents and young women. An assumption is typically made, until symptoms are profound enough to require otherwise, that whichever symptom the patient presents is likely attributable to a cause of the specialty to which they were referred. A further delay of diagnosis occurs when the stamp of "treatment resistant" is applied because the patient does not respond to the assumed cause-related treatments; they are then taught to tolerate and exist alongside the pain or disorder.

There are a wide variety of factors which have contributed to the invisibility of endometriosis in adolescents and young women. The pharmaceutical industry, medical institutions, and traditional schools of psychology have all contributed to the lack of awareness and delayed diagnosis of endometriosis, beginning with adolescents. Professional bias and the recent indoctrination of the dialectically opposed *non*-judgmental stance have *both* exacerbated the situation. Parents' culture, upbringing, and societal assumptions regarding teens have further condemned the female adolescent to suffering in silence from endometrial pain. And finally, as we come to the last nail in the coffin, the phenomena Occam's razor, the theory of narrative causality, and the law of the instrument all have a role in the prevention of timely diagnosis of endometriosis.

Having amassed over 30 years of observations from several vantage points in medical care, this chapter is largely the culmination of realizations regarding the criterion-based, and perhaps even unethical, mistreatment (including neglect) of female adolescent patients in the world of mental health medicine. Sadness at the marginalization due to that which is either invisible or not impacting enough for the professional to have even the possibility of consideration leads to the purpose of our chapter. Our aspiration is to raise awareness of the need for accurate and comprehensive care in the treatment of female adolescent emotional dysregulation related to endometriosis and associated reproductive system disorders not only for the mental healthcare field—psychiatrists, psychologists, and the counseling profession—but even more importantly for all fields practicing some level of individual and family psychotherapy, from pediatricians and internists making referrals to counseling to those primarily geared toward the public sector, i.e., social work.

If all you have is a hammer, everything looks like a nail. – Abraham H. Maslow

Pharmaceutical Research and Medical Schools

During the course of their medical education, aspiring doctors are privy to an education in and a comprehensive understanding of interdependent and co-existing anatomical and physiological systems. As physicians specialize, they still (ideally) have the fundamentals of each of the other disciplines in medicine in order to recognize symptoms and make appropriate referrals.

However, why are educational seminars geared toward physicians only within their chosen specialty and not to physicians of other specialties or non-physician professionals?

Partly the answer lays in pharmaceutical companies. Pharmacological education serves to raise awareness of symptoms that professionals may not be aware of as contributing to specific diseases. I have watched over the years, despite psychotherapy being the field that spends the most amount of clock time with patients, drug reps from pharmaceutical companies have systematically removed anyone but physicians at their drug education seminars and dinners. The average psychotherapeutic clinician is typically disallowed from attending informational events. The awareness of symptomology arising from medical conditions is unavailable due to several factors—this being but one. At the APA conferences, booths abound with information about the latest advances in psychopharmacology from companies that are sponsoring various seminars and talks. Pharmaceutical booths have not been present at the numerous conferences of the Georgia Psychological Association, the Licensed Professional Counselors Association, or the National Board of Counselors in my past 20+ years of attendance. In personal experience, the ability to make physiological connections with emotional dysregulation through pharmaceutical information and progress at conferences has been limited to psychiatrists' meetings.

Divorce: Medicine vs. Psychology

Over time, as the medical field has progressed, the academic divorcing of head vs. body, brain vs. bones, and—perhaps the worst offender of all terminology—mental vs. physical has proliferated. The pathologizing of emotional expression has burgeoned. Why? We look at two historically prominent reasons.

The historical derivation of the word "hysteria" is borne of the Greek root *hystera*, the word for "uterus" in ancient Greece; ailments of the female persuasion were treated with physical medicine at that time [1]. Fast forwarding to the nineteenth century, Charcot's use of the word "hysteria" became synonymous with "neurosis." Unfortunately, the twentieth century brought about Freud redefining the word neurosis as emotional and/or behavioral dysregulation due to past trauma [2]. The word in and of itself has gone from being utilized as an organic explanation of symptoms to a pejorative description of inappropriate or egregious emotionally driven behavior, currently mirrored quite depreciatively by the diagnostic category of borderline personality disorder in the DSM IV (proposed, but unresolved as of yet, as emotional dysregulation disorder in the DSM 5).

As such, the beginning of the twentieth century allowed Freud to set the stage for the vehemently denied but aptly visible progressive non-treatment and mistreatment of female consumers in medicine. Anything that could not be proven with "real" medicine or that which had unexplainable symptoms was left to be labeled as "hysteria." Present day has promoted this through the pejorative labels of "drama queens" for adolescents and women who are condemned to psychiatric/psychological treatment for undiagnosed medical conditions such as endometriosis.

Secondly, when neuropsychiatry was a unified field, emotional/mental illness was treated by physicians as if it was a result of organic disorders. Upon the division of neurology and psychiatry, neurologists focused on the *physical* diseases of the brain, and psychiatry delved into treating emotional and behavioral disorders [3]. Increasingly, psychiatric medicine has been devoid of investigation into causes other than environment and circumstance for emotional dysregulation. A major contributor to this transgression is due to third-party payment as it has diminished the time allotted for a physician to examine causes of symptomology prior to administering a diagnosis. Progressive evolution of psychiatric treatment has resulted in pharmacological intervention directed toward raising emotional tolerability and reducing vulnerability to stressors instead of addressing the factors that led to heightened emotionality in the said circumstances resulting from the lowered pain thresholds due to physical illness.

Between forces inviting the increasing invalidation of female symptoms and a negation of the connection between physical illness and emotional challenges, the resulting obstruction in the evolutionary process of research has translated into defending a deficiency in comprehensive gender-based medical care which in turn directs the lack of (pursuing) gender-inclusive and conscious medicine—again, beginning with research.

Freudian psychoanalysis was/is not about making patients "normal" or even about curing them. Rather its function is/always was to reveal deeper insights into a person's psyche. Current-day psychological practices are more solution focused, and yet, the pervasive nature of an exploratory mindset has resisted change. Medicine, which is designated to be physical healthcare, has a curative mentality focused on disease-free functionality. Psychology/psychiatry—mental healthcare—has a treatment/management outlook directed toward adaptation to and acceptance of normalizing behavioral pathology and its ensuing emotional symptoms.

US statistics for 2016–2017 show 112,040 mental health and substance abuse social workers, 139,820 mental health counselors, 91,040 substance abuse counselors, and 42,880 marriage and family therapists; they also show 25,250 psychiatrists and 166,000 clinical and counseling psychologists [4]. By separating "physical medicine" from "mental healthcare," the latter has become a hammer; most profoundly this is noticeable with psychotherapists—despite being the most widely utilized profession in the treatment of behavioral and emotional disorders (especially with the burgeoning shortage of psychiatrists). The hammer mentality dictates that symptomology is attributed to—and limited by—the disorders in which the professional in question has been educated. The divergence of schools of thought has led to terminology which indicates that physicians practice medicine and

psychotherapeutic professions engage in management. Though the majority of "physical" illness/disease frequently has an emotional or behavioral presentation, the counseling profession has never been included in the equation of holistic care. Thus, when adolescents—and especially those with intermittent symptoms and pain—become nonfunctional or dysfunctional enough for their parents to seek treatment, it is viewed more often as malingering, behavioral defiance, truancy, drug use, etc.

Given that counselors typically refer patients to psychiatrists when the symptoms do not respond to behavioral remedies and protocols, it becomes the responsibility of the psychiatrist to identify the primary physical cause of emotional dysregulation instead of solely medicating with antidepressants; it is in their purview to refer the patient for additional evaluation to other specialties. However, the ability of a psychiatrist to obtain the whole picture and case manage the primary causes of dysregulation is at best limited or nonexistent due to time and access. Therefore, it falls on the counseling profession to be educated enough to recognize the need for evaluation of the primary cause of the emotional dysregulation. The most responsible treatment of a patient dictates an exhaustive physical examination.

Counselors/psychologists spend the greatest amount of time with the patients and are routinely referring patients to psychiatrists and psychometric testing for evaluation of emotional dysfunction that is not responsive to behavioral measures. It is only when we see behaviors that either prevent a patient attaining self-desired or societally designated goals or we see behaviors that interfere with others' daily functioning, that these disruptive behaviors become a cause for urgent treatment. A primary course of action for the patient not responding to a clinician's behavioral interventions is to refer to a psychiatrist who is trained to quash the said disruptive behaviors with urgency by utilizing pharmacotherapy. Unfortunately, when pharmacotherapy is not as efficacious as desired, sadly I have not, in the past 30 years of practicing medical care, personally seen a psychiatrist send a patient to a physician in a different specialty for further evaluation outside of a few isolated cases.

When psychiatrists and counselors experience burnout or frustration at a patient's seeming lack of progress, the patient is often termed "treatment resistant" and referred to Dialectical Behavior Therapy (DBT)*. If clinicians utilized "wrong diagnosis" instead of branding patients as "treatment resistant," then professionals would begin considering other options outside of their specialty.

The limitations and long-standing biases of clinician education have lent to interpreting all pain as psychological. While counselors are not required to complete rotations in every specialty, it is important to teach psychotherapists how to recognize the possibility of medical roots, take complete medical histories, make connections, and refer to appropriate specialists. Because clinicians see only what they look for, all pain, including physical, can be too readily seen as a means for secondary gains affecting recommended treatment options. Diagnosis is based on inclusion, but more importantly, perhaps, exclusion must be investigated. *Communicating to family members that pain is due to secondary gains has lent to the general public believing pain is exaggerated and can be dealt with using talk therapy.*

**Karen* experienced menarche at age 12. From the very beginning, there were extremely heavy flow and severe cramping for 2–3 days that would render her bedridden. Vomiting and headaches were the norm. Her moods would be volatile and extreme in the 7–10 days prior to monthly menses. Impulse-driven behaviors of self-harm (cutting, burning) would escalate the closer she was to beginning her period that month. As she matured, intercourse continued to be extremely painful. For the next 20 years, her emotional lability instigated maladaptive behavioral patterns which in turn rendered her suicidal leading to psychiatric in patient hopsitalization multiple times throughout the year; she earned the ultimate label of borderline personality disorder, treatment resistant. The young woman also had a history of being labeled with schizophrenia, major depressive disorder, generalized anxiety disorder, bipolar disorder, etc. She experienced severe fatigue and chronic pain. She had documented irritable bowel syndrome and severe allergies along with asthma. Despite the evidence presented for autoimmune disease, pelvic pain, and abnormal severity of painful menses, she had never once been seen for a full reproductive, endocrinology, or gynecology consult.*

Why? In this case, there was a history of sexual abuse and molestation that began at age 12 and lasted to age 15 which became the focal point of the cause of all emotional and behavioral symptomology. This young woman experienced a delay in diagnosis because the assumptions made by therapists followed her and psychiatrists failed to do their own evaluative examination inclusive of quality of life-threatening conditions, symptoms, limitations, and life-threatening behaviors [5].

Traditional Psychotherapy and DBT

While medicine is focused on current causes of illness, traditional psychotherapy centers on reliving past environmental stressors and threats to identify causes of presenting complaints. Traditional counseling programs do not teach students to "think outside the box" in terms of making differential diagnoses, including medical issues or conditions that could cause presenting symptoms. The adolescent/young adult females (ages 9–26 as we define them) with undiagnosed endometriosis or associated disease at our DBT clinic usually are at the mercy of a variety of symptoms including severe depression, unremitting anxiety, primary or secondary sleep disorders, anger outbursts, apathy, anhedonia, social anxiety, and PTSD symptoms that are potentially devoid of a discernable trauma (or worse yet attributed to an incident which has been blown up exponentially by practitioners in designing the cause for the emotional dysregulation) and the pervasive label of "lazy." Diagnostically, the oft used labels entertained by psychiatric providers include borderline personality disorder or bipolar disorder, which appear to be used interchangeably. (Mood lability of BPD often is produced by interpersonal sensitivity, whereas mood lability in BD tends to be autonomous and persistent [3].) Usually, by their later teen years, adolescents have been inundated with a host of other

diagnoses as well, including the disorders—major depression, generalized anxiety, obsessive-compulsive, oppositional defiant, etc.

While Dialectical Behavior Therapy (DBT) will help modify behaviors, quite possibly for the first time, generalization of skill sets is already challenging due to the increasingly changing landscape and expectations for teens—especially for the adolescent suffering from undiagnosed/untreated endometriosis. Even when the emotional struggle is validated and treated, without the resolution of the root physical cause, patients will continue to put out fires throughout their lives, instead of bringing the arsonist to justice, once and for all.

Regrettably, mental healthcare professionals generally take presenting symptoms and not the *absence of symptoms* to make a diagnosis. Additionally, symptoms outside of the scope of the professional's training are ignored as significant contributors. When an adolescent comes in with parents reporting mood swings, apathy, lethargy, and an unwillingness to go to school, we often observe that the positive symptoms lead to the diagnosis of bipolar disorder, major depressive disorder, anxiety, oppositional defiant disorder, and the like; worse yet, if the symptoms do not line up with a specific diagnosis, the addendum "NOS—not otherwise specified" is applied. The egregiousness of this resides in the absence of consideration of the possible existence of unknown symptoms that prompt the complaints (which are also denied a voice due to parental issues, mentioned later). Typically, if the child is too young to be assigned a label, they are predictably given the diagnosis with an additional addendum—"traits" or "borderline personality disorder traits, not otherwise specified."

Traditionally, psychotherapy patients are only asked about environmental or situational events. There is largely an absence of examination of the nature of mood swings: Are they cyclical? When is the worst of it during a 4-week cycle? Is there a 2–3-week period of trying to pick up the pieces of their destruction from the last time the mood swings occurred? Are there other concurrent symptoms, such as (physical) pain, and if so, where? Is the apathy due to cumulative exhaustion from withstanding physical pain?

Academically, DBT clinicians are highly specialized even further. DBT uses distress tolerance techniques to manage the emotional pain, emotion regulation techniques to change the impact of the emotional pain's effect on quality of life, and/or an excision of the circumstances to remove the factor(s) percieved to be causing the egregiously unwanted behaviors. Unfortunately, the average DBT clinician focuses almost exclusively on the first two strategies. Even with the most efficacious of DBT psychotherapeutic applications, practitioners (because they are general counselors who have subspecialized) are not schooled in looking for the "physical"/medical basis of a symptom and, therefore, are too easily accepting of psychosocially disruptive symptoms. Additionally, the majority of psychotherapy practiced nationally is everything but DBT much less correctly applied DBT[B]. Furthermore, without the knowledge of what to do, the ability to investigate physical illness as a cause of emotional disturbance is limited to the educational interests and exposures of the provider.

DBT is an extremely rigorous application of behavioral principles taught through a vehicle of skills-based behavioral change. Because DBT was originally designed for borderline personality disorder, many adolescents with endometriosis, PCOS, etc. will be referred for DBT as these medical conditions often manifest through extreme emotional dysregulation, especially cyclically (which, when left uncharted or untracked, appear to manifest haphazardly at best— analogous to BPD).

Clinician Bias and Non-judgmentalism

In asserting relatability, many clinicians in mental health that I have encountered have purported to being "one of the most non-judgmental people." Being "non-judgmental" is the Nobel Prize of behavioral traits to be owned and exhibited by a clinician. In the effort to judge and assert oneself as relatable, accepting, and open, it is all too easy not to see a patient's symptoms in an absolute, unbiased, tabula rasa state of mind. Significant non-psychiatric symptoms can be too readily missed. Assumptions based on the clinician's experience can too often be the culprit in mis-gauging the true strength of a patient's distress despite evidence to the contrary. Overt similarities have the danger of overshadowing covert discrepancies. All too easily, other critical symptoms may be overlooked. Moreover, by the time one has become a psychotherapy clinician, they are also judging the adolescent through the eyes of an adult—not one of a child. Time allows for seemingly inconsequential memories to dull, and often, even the most horrific of traumas when resolved will soften in their intensity. This can contribute to downplaying the impact of a patient's pain. Also, there can all too readily be a clinician's bias toward judging adolescent's pain as "dramatic" if they themselves were treated or labeled as such, particularly if the symptoms of invalidation have not been resolved for the clinician themselves. Either way, there is a danger in attempting to circumvent the notion that an adult can comprehend the depth of an adolescent's pain from having been one themselves.

When we only see things as we are, then we become a hammer.

> A lot of what passes for depression these days is nothing more than a body saying that it needs work. – Geoffrey Norman

Borderline Personality Disorder (BPD)

In looking at endometriosis, we face certain factors that make patients vulnerable to not being taken at face value regarding the severity of their symptoms. First, it is age. Repeatedly in our clinic, upon conducting a medical history, we have observed either origination of or a serious exacerbation of severe emotional symptoms in the year prior to or the year of menarche. Because the mental health field has deigned it incorrect to assign many psychiatric diagnosis to patients before

adulthood, symptoms are often attributed to "hormonal changes." Unfortunately, and quite paradoxically, these are not investigated to be attributed to their actual cause and are instead used to inform psychiatric treatment. Secondly, the struggles of transition into high school serve to normalize pathological emotionality until and unless the dysfunction of the individual disables routine family functioning, at which point an intervention to control the behavior is sought. And, given that endometriosis will not show up on the average set of laboratory tests ordered, the adolescent is deemed mentally unstable and is led to psychiatric/psychological treatment.

Adding insult to the injury, it is stunning that when a patient is "treatment resistant," it is because their symptoms will not respond to the provider's knowledge base, thereby condemning them to be egregiously labeled "a borderline." But, because adolescents cannot be technically labeled as such, they are often sent to clinicians as having "borderline traits." When we hear the following symptoms, early awakening; excess sleepiness, insomnia, or restless sleep; excessive hunger or loss of appetite; restlessness; irritability; social isolation; lack of concentration; slowness in activity; and weight gain or weight loss, what comes to mind? Depression? If we hear of restless thoughts and an inability to concentrate, we jump to what? Attention deficit disorder (ADD)?

Here are some of the characteristics that lend to a patient being assigned a label of borderline personality disorder. However, these same symptoms are regularly seen in young women with endometriosis:

Borderline personality disorder	Endometriosis
Fear of abandonment. People with BPD are often terrified of being abandoned or left alone	People living with the chronic pain of [undiagnosed] endometriosis are often fearful of having no one to take care of them or their needs
Unstable relationships. People with BPD are constantly challenging their relationships	The young woman with endometriosis will often have unstable relationships that are based on an unequal dependency, often leading to feelings of resentment in relationships. The sufferer may resent others for not helping as she desires the help or for not helping enough to alleviate the suffering. Loved ones may grow to resent the inability to satisfy/rectify their loved ones' pain
Unclear or shifting self-image. BPD sufferers have an unstable sense of self based on patterns of invalidation throughout life	When endometriosis delineates the parameters of the emotional portrait of an individual, each week of a cycle is generally defined by different capabilities. This sets the patient up; most individuals are judged in potential by their highest capability; unfortunately, sufferers usually meet that mark 1 week out of 4
Impulsive, self-destructive behaviors are a critical defining behavior in BPD—it is seen in patients who are driven to impulsive behaviors to get their physical pain noticed	For the undiagnosed, emotionally vulnerable teen, impulsive behaviors that materialize to self-regulate emotions and enlist help are a mainstay of the diet

Borderline personality disorder	Endometriosis
Extreme emotional swings are another defining characteristic of BPD	Each week of a 4-week menstrual cycle for a sufferer of endometriosis will bring about severe, seemingly unexplainable mood lability
Chronic feelings of emptiness are yet another hallmark feature of BPD	When chronic pain patients have unmet needs for validation and relief, a sense of worthlessness abounds
Explosive anger is a significant element as well of BPD	The emotional havoc wreaked by endometriosis predictably results in explosive anger, pleading, and withdrawal—as needs for relief are not met and invalidation escalates

**Diana* by her mid-20s had spent her life battling large emotions that strained relationships alongside severe physical pelvic pain during her menstrual cycle. The heavy tide of emotions would often cause great strain in intimate relationships to the point of physical, verbal, and emotional abuse—inflicted by her on her boyfriend. Very visible was the tortured desire to learn coping skills and change her reactions. Also evident was the waxing and waning of her ability to do so. A diagnosis of endometriosis brought validation; she was not "crazy." This made it easier to understand the desperate nature of her impulses and find the willingness to fight them. Adding insult to injury, because of heavy medical investigation into the inability to readily employ taught methods, a tumor of the pituitary gland was discovered. Given the anatomical issues, her physiology was completely compromised. We did not label her "an endometriosis" or "a tumor." And yet, she has been labeled "a borderline"—due to the emotional vulnerabilities exhibited owing to the behavioral manifestations of surviving undiagnosed endometriosis coupled with the existence an unknown tumor.*

We don't see things as they are. We see them as we are. – Anaïs Nin

The Role of Shame

In medicine, for example, when a patient with endometriosis comes in, [one assumes] the general plan is to take a medical history, identify the problem, run the appropriate scans, acquire the appropriate labs, conduct a medical examination, and chart a course of action be it surgery, medication, or whatever the physician deems appropriate. Family history is significant in that it may enable earlier or more accurate diagnosis from the patterns in the maternal lineage. Shame is not imposed on an adolescent's mother for passing down hereditary factors that cause endometriosis. Nor is the adolescent condemned for somehow allowing herself to succumb to the endometriosis. "Blaming/shaming the mother" is a standard joke in the psychotherapeutic field. Thus, psychotherapeutic focus and care is on ascertaining how situational events produced the symptoms affecting an individual's emotional functioning. The hunt begins to find causes other than what the patient has done, in an

attempt to alleviate the guilt and shame that a patient has caused their own problems in the hopes that this freedom will allow for the patient to heal themselves. This takes away from a consideration of exploration of physical anomalies.

In a counseling assessment, the family history of mental disease is usually one of the first things to be addressed in the pursuit of ascertaining that the patient's symptoms will readily fit into some criteria needed to check off a box. Following that, the psychosocial family dynamics will be examined to see how family and parental interactions are leading to or sustaining the adolescent's behaviors—leading to feelings of shame in parents. And then, the questions of what the adolescent does not know how to do by way of coping are addressed through basic acceptance-based techniques of self-soothing or distraction or change techniques involving identification of stressors, problem-solving, and behavioral and reactionary change methods.

Historically, adolescent patients with undiagnosed reproductive disorders have most typically presented with self-harm behaviors at our clinic. Unknowing of their own physically diseased or disordered state, they readily tell us of the shame that they feel being unable to cope with their stressors and, more often than not, letting "everyone down." Particularly heartbreaking, in traditional counseling, there is largely the tendency to encourage the adolescent to "do what's right" for the sake of the family and *then* themselves. Even though shame is not investigated nor entertained as a supporting audience to validate the continuation (or the need for discontinuation) of the self-harm in DBT, unfortunately, the behavioral clinician still does not have the education necessary to investigate for endometriosis.

Because self-harm^{D} is partly due to an effort to regain a perception of self-control, once endometriosis is identified and successfully treated, ideally, hormonal homeostasis will be reinstated. The adolescent will no longer have to self-harm in an effort to regulate the experience of out of control emotions that are occurring independent of environmental factors.

Another issue is due in part to adolescents not having a barometric gauge for what is normal and what is not with their reproductive organs. They either are too embarrassed to ask questions or, moreover, generally are unaware of even what questions to ask. A former patient ended up in the ICU from an UTI, all because the adolescent did not know the basics of sexual hygiene and kept dismissing her symptoms.

The social invisibility of endometriosis occurs on several levels. Adolescents often do not feel comfortable talking to adults, be it their mothers or their doctors. Mothers normalize pain that is pathological. On the other hand, they also pathologize reactions to and behaviors prompted by pain. Practitioners are either unaware or dismissive of the importance of symptoms that could point to endometrial disease.

Occam's Razor May Be Dull

A critical look at Occam's beard suggests that propositions must be abstracted from some type of concrete reality. Therefore, given that depression (and anxiety, borderline personality disorder, bipolar disorder, oppositional defiant disorder, etc.) *should*

be a diagnosis of exclusion because there are no definitive laboratory tests nor scans to positively identify a diagnosis of such, there must be a valid search for the absence of proof to justify it. This requires a sufficient history to be taken in context of not only circumstance but age, physical developmental difficulties, and the like. And unfortunately, mental health providers are excluded from the awareness, much less the ability to collect all of elements necessary to make a diagnosis founded on an elimination of factors as well as a consideration of the presenting sequela.

One of the most common scenarios in our clinic—at a rate that is increasingly alarming—over the past 30 years is of the adolescent female patient presenting with symptoms that have begun in the timeframe of 1–2 years pre-menarche to 1–2 years post-menarche. It is disturbingly frequent that especially without a dysfunctional family dynamic or any traumatic stressors, the destructive symptoms are attributed to some variant of an adjustment disorder; the adolescent is labeled with depression, anxiety, or BPD—and the professional calls it a day. (Upon scrutiny of those of our patients which were referred to gynecology/endocrinology/reproductive medicine, it has been frighteningly close to a 100% of the time that the primary illness is some form of a reproductive system disease—and in the rare event that it is not, it is typically PMDD, PCOS, or one of the related cousins—PID and IC.) *This has created a system whereupon "wrong diagnosis" is rarely if ever entertained as a reason for treatment failure and "treatment resistant" is the label plaguing our teens to the exclusion of further evaluation.*

Efficiency in medicine may well have dulled Occam's razor.

Parental Obstruction and Adolescent Powerlessness

A particularly covert confounding factor in the early and accurate diagnosis of pain is the parents speaking for the child. In their advocative zeal to relieve (their?) the child's suffering, they too overlook the fact that we see things as *we* are. Not as *they* are. Between parental expectations and the desire to project an image satisfactory enough for social acceptance, there is the struggle to ascertain parental approval through excellence and achievement yet be established as one of a group and not be singled out. A teen with a focus on being seen as interesting to peers can lead adults to view the adolescent female as a "drama queen." Over time, this may cause the parents to disregard genuinely problematic symptoms. Additionally, in homes experiencing discord or dysfunction, a teen may become focused on parental approval or maintaining peace in an already distressed household. Not wanting to be an additional stressor for the family unit, she will negate or sublimate her own needs and avoid by any means necessary bringing the problematic symptoms to the forefront.

Over time, if a parent, typically the mother in our clinic, has invested a substantial amount of time attending to the adolescent's needs, she may feel the need to take charge and control the narrative. Because no one can experience anyone's pain better than the person in pain themselves, any iteration by anyone other than the patient is likely to leave out information that is crucial for an accurate diagnosis. Much of

the time, seeing an adolescent without parental influence in the room yields much more insightful information unless the teen is habituated to being shut down. And yet, mothers are often wary of allowing their children to interact with medical professionals alone.

A secondary factor revolves around the history of a mother who has been victim to undiagnosed or unrelieved endometrial disease herself. Mothers, often suffering themselves, will normalize excruciating pain as something to be tolerated. Often, the daughters of the said mothers will hear a statement akin to "sweetie, it's just something we women have to put up with" as they try to spare their daughters an unending cycle of gaining and losing hope for relief nowhere to be found.

> If you think education is expensive, try ignorance. ~ Derek Bok

Costs

There is a high cost associated with undiagnosed endometriosis in adolescents. When referrals are made primarily for mental healthcare to treat the emotional dysregulation which is due to the behavioral manifestation of physical disease, the price tag is high and becomes a situation of throwing "good money after bad" however unwittingly.

School and Socialization

Pain leads to anxiety. Anxiety about when the pain will come. Anxiety about how the adolescent will be perceived by her peers. Anxiety about whether or not she will be understood and believed. Anxiety about being able to fulfill obligations. Anxiety about being able to engage in the normal social activities with peers outside of school and extracurricular activities at school.

A lack of effective treatment, not being taken seriously, and an unexpected inability to participate in activities due to unpredictable pain—either because menstrual cycles are not consistent or because pain is not consistent cycle to cycle, all lead to (internalized) anger.

Anger with no solution in sight yields a depressive state, leading to increased withdrawal and isolation. It can also lead to self-medication via drug use or alcohol abuse. The pattern between depression, anger, and anxiety is cyclical in nature. School equals socialization for teens, and the lack of such opportunity further leads to isolation, thereby causing withdrawal and manifesting as symptoms of depression.

The educational cost is multi-fold. Missed days in school are an interruption in education and damage prospects for long-term education. When missed days become excessive, they can eventually lead to academic failure which will prevent participation in extracurricular activities owing to the inability to attend practices,

meetings, and events due to enormous pain rendering the adolescent to her bed. Long absences will also accrue from the impulsive behaviors that have developed as a coping mechanism which ultimately lead to hospitalizations at mental healthcare facilities.

Family

In the family unit, resentments can begin to build. Other children may find the family's activities curtailed by the adolescent suffering from the pain of undiagnosed endometriosis. Resentments can begin to build between the suffering adolescent and her siblings. In turn, this makes it difficult for parents to manage the needs of the other children, thus leading to *their* resentment of the suffering child. Too often we see discord between parents whereupon one feels that the other is "coddling" the child.

Financial

Various entities are affected financially by a delayed diagnosis of endometriosis. Mental healthcare is typically more out of pocket than not, and we have watched as insurance companies are loathe to pay for outpatient treatment although they do not mind paying heavily for recurrent inpatient stabilization. Families spend decades paying for mental healthcare, to the neglect of other family members' needs. Lessons, vacations, and the lot are denied because funding must go to emotional management of the suffering teen. Because of a lack of parity in healthcare for illnesses deemed to be originating from the brain vs. the body, it is incredulous that the primary direction of investigation then is not for "physical" illness leading to emotional dysregulation. Insurance companies would surely save money if they were to require investigation to treat the medical causes of mental health disorders as a first line of care.

Solutions: Ending the Invisibility of Endometrial Disorders in and by the Mental Healthcare Community

Medical Industry Responsibility: Maintenance vs. Cure

The mental health industry emphasizes that asymptomatic people are "in recovery." However, even an asymptomatic cancer patient after 5 years is "cured." The medical industry must make the mental healthcare field an equal member in

holistic care and emphasize treating the root cause of emotional dysregulation, not just the symptom, as it relates to quality of life-threatening behaviors. Then only will the placation focus on lessening the impact of emotional dysregulation tame.

Pediatricians

A teen's doctor will generally make an initial referral for mental healthcare services. As a matter of routine, for the patients at our clinic, we find that the pediatricians in general have not investigated reproductive or endocrine disorders. The ability to develop and apply an algorithm to increase awareness of the root cause of emotional dysregulation needs to be applied to all physician specialties that routinely care for children.

Mental Health Record Keeping: Tracking

The pivotal piece of information not available in standard therapy but is required in DBT comes from a "diary card" that tracks several emotions, daily, through the months of treatment. Here, causal, contributory factors are identified in the escalation of harmful behaviors which are mood dependent. These are tracked in relation to sleep patterns, eating schedules, etc.

Because the preponderance of the adolescent and young adult females seen in our clinic are found to have severe, undiagnosed hormonal issues (not that older females have been particularly exempt) such as those caused by endometriosis, the diary card can be the most crucial tool in identifying the cause of emotional dysregulation. Most importantly, in our clinic, we require females to track the day of the menstrual cycle in order to identify the patterns in behavior and emotions along with physical pain that determine whether further evaluation from an endocrinologist, gynecologist, psychiatrist, or rheumatologist is warranted. The information needed to suggest consideration of endometriosis or reproductive system illness outside the purview of psychotherapeutic interventions is dependent on this tracking and analysis.

Upon questioning and tracking emotions with menstrual cycles, invariably it becomes increasingly evident that for many, the worst of the symptoms will often occur during the 7–10 days before the menstrual cycle and that our patients spend the next 20 days attempting to "clean up the mess"—the havoc wreaked in their personal relationships with family, friends, and teachers—never quite returning to baseline before the next cycle begins.

Education for Mental Health Professionals

Education in holistic care requires symptom awareness beyond the scope of the particular practitioner's field. All schools of education that produce practitioners who intend to treat emotional dysregulation must have mandated education in organic bodily illnesses. From AIDS to zinc toxicity, there are an incredible number of illnesses that include the manifestation of emotional dysregulation as part of the sequelae of the illness. Given the impossibility to be schooled in the signs and symptoms of every illness, there must be an algorithm established to, at the very least, point a psychotherapeutic clinician to the appropriate specialty for further analysis. Developmental analysis of symptoms is crucial in the identification of the probability of undiagnosed endometriosis, PCOS, PMDD, UF, etc.

Proposals for immediate allowance of change:

- Refer to emotional dysregulation as a symptom of illness in the brain or body. Identify which parts of the brain are active in the malfunction. Look for bodily causes—endocrine, hepatic, reproductive, cardiac, lymphatic, etc.—that may be generating changes in the brain. Brain science is perhaps the least developed specialty in medicine. Psychiatric/psychological medicine must be a specialty of *ruling out disorders* before the assumption is made that there is non-brain-induced physical system cause for emotionally dysregulated behavior—*especially* in the face of severe environmental stressors.
- Because there are no tests able to identify the absence of an illness, we should assume that for, at the very least, symptoms not otherwise encapsulated within a tidy range for lab values, psychotherapeutic interventions must be outlined based on symptoms of inclusion *and* exclusion.
- In the absence of mental disorder or disease in a family unit, there should be first an immediate ruling out of possible medical conditions, no matter how unlikely they may seem. After all, someone has to be the person that makes up the 1% of all the "rare" disorders.
- Lab values are norms for lab values. Lab values are not people. The presence of subclinical lab values or "minor" findings should not negate the pain experience of an individual. People are not numbers.

Above all, adopt a curative mentality.

We have ceased looking for that which we do not know, and what we do know is being ignored. How do we validate the existence of endometriosis and relieve the burden on the adolescent, her family, friends, teachers…when one hand is clapping alone? This is akin to the koan that asks: if a tree falls in the forest, does it make a sound? What we do know is that it takes two hands to produce a sound. Medicine and psychology must re-engage as a comprehensive entity.

Glossary

A. *DBT:* Dialectical Behavior Therapy is an advanced form of cognitive behavioral therapy that utilizes the dialectic of acceptance (validation of tolerating distress) with change (implementation of behavioral techniques) to providing sustainable relief for the multiply disordered emotionally dysregulated patient. DBT is most effective in teaching the ability to manage painful emotions and decreasing conflict in relationships. DBT was developed for those with under-controlled behaviors that led to chaotic life patterns. Randomized, double-blind studies have repeatedly shown efficacy in eliminating parasuicidal behaviors and suicidal ideation along with behavioral patterns that can lead to these. Core skills taught are:

   – *Mindfulness: the ability to stay present and focused.*
   – *Interpersonal Effectiveness: the ability to meet relationship and self needs without compromising relationships.*
   – *Emotion Regulation: the ability to choose the type, intensity, and duration of an emotion.*
   – *Distress Tolerance: the ability to tolerate unwanted emotions without making things worse or without trying to escape from them.*
   – *Walking the Middle Path: these are skills on shaping behavior and finding balance.*
   – *Radical Openness: skills for over-controlled behaviors of fixed mindedness and fatalistic thinking specific to GAD, MDD, OCD, PTSD, etc.*

B. *NON-PROTOCOL DBT:* A brief explanation for the non-mental health clinician: Non-Protocol DBT (referred to as "*informed* DBT") is not forcibly regulated by the Licensed Professional Counselor Association or the National Board of Certified Counselors like medication in a bottle is by the FDA. Therefore, the non-regulated version is generally as effective as supplements on the market; there is no standardization practitioner to practitioner (bottle-to-bottle) much less skills therapy class-to-class (pill-to-pill). "Informed" DBT therefore is as effective as the practitioner is on any given day, with changes that are typically not sustainable. However, akin to being in a doctor's office, patients often balk at the commitment and compliancy needed for sustainable change by taking their pharmaceutical medications daily (Full Protocol DBT) and correctly (required DBT assignments). They will settle for the temporary daily improvement with a supplement—when they feel bad enough to remember taking it. By and large, it's when the supplement doesn't cure the cancer—or worse yet creates toxicity (total quality of life disruption)—that the patient will inevitably end up in conventional medical care. When informed DBT fails, and the patient resorts to self-harm behavior, then, inevitably, parents will commit to the compliancy schedule required of Full Protocol DBT.

C. *EMDR:* It is a highly controversial technique claiming to obtain, neutralize, and resolve traumatic memories considered to be at the root of psychological disorders.
D. *SELF-HARM:* There are several functions for physical self-harm (cutting, burning, etc.). Self-harm behaviors serve to relieve external pain with internal pain. Well documented is that just as many a person does not categorize the feeling as "pain" during tattooing, nor does a self-harmer. There is typically a "high" associated with these behaviors. (This is substantiated by successful treatment with naltrexone [6].) Contrary to conventional wisdom, self-harm is rarely a "cry for help" as it is generally hidden until accidental discovery [7].

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Chapter 20
Adolescent Endometriosis: Fertility Outcomes

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Introduction

A chapter on fertility outcomes in a book on adolescent endometriosis may sound rather unusual. Adolescents with endometriosis usually present with pain symptoms [1]; contraception rather than fertility advice is more likely to be required. However, the management – or mismanagement of endometriosis – may have a significant impact on future reproduction; hence, fertility should be kept in mind when decisions are made on treatment options. The questions related to fertility when counselling teenagers or their parents may include the following:

- Will she be able to get pregnant and have a family in the future?
- Which treatment option would give her a better chance of fertility?
- Would surgery preserve fertility?
- Could surgery cause infertility?
- Does early surgery lead to better fertility outcomes?
- Should repeat surgery be avoided to preserve fertility?
- Should she freeze eggs?

As with many aspects of endometriosis, there are no clear answers for any of these questions. One can only extrapolate information we have from older women, but without prospectively collected data, questions will remain on their validity.

In this chapter, these questions will be expanded, available data will be summarized, logical speculations will be made from the currently available data, and knowledge gaps will be highlighted.

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Endometriosis and Infertility

The association between endometriosis and infertility has always been controversial. While it is easy to explain infertility in advanced (moderate or severe) stage endometriosis when there is significant distortion of the pelvic anatomy, impact of early (minimal or mild) endometriosis on infertility has been questioned as the pelvic anatomy remains mostly normal.

It appears that women who have a diagnosis of endometriosis are twice more likely to experience infertility in future life [2]. The Nurses Health Study II prospectively collected information, and data from women aged 24–40 years at the age of enrolment were analyzed. Women with a history of infertility at enrolment were excluded. After 16 years of follow-up, women who were diagnosed with laparoscopically confirmed endometriosis had a twofold greater risk of infertility compared to those without endometriosis. This is probably one of the very few evidence-based data that we can give to the adolescents to inform them of their future risk of infertility.

Most published case series on adolescent endometriosis report on pain and disease recurrence outcomes. However, two articles by Audebert et al. [3] and Ventolini et al. [4] reported some fertility-related data.

Ventolini et al. [4] reported fertility outcomes in 28 adolescents who were followed for a duration of 8.6 years. Endometriosis was diagnosed at laparoscopy, and all patients were treated with a combined oral contraceptive which was taken continuously. Twenty-two of the 27 patients who were followed had a desire to conceive. The fecundability rate which was defined as the probability of achieving a pregnancy within 1 year period was found to be related to the stage of endometriosis: 3/4 (75%) in stage I, 6/11 (55%) in stage II, 3/12 (25%) in stage III, and 0/1 (0%) in stage IV. It must be noted, however, that the number of patients who had a desire to conceive was 3 in stage I, 9 in stage II, 10 in stage III, and 0 in stage IV, indicating that 100% in stage I, 66.7% in stage II, and 30% in stage III conceived. Six of the 22 patients apparently had additional treatments, but these were not specified.

In the article by Audebert et al. [3], out of 55 adolescents aged 12–19 years, five apparently had a history of infertility. All patients were treated with excisional surgery, and antiadhesion tools were used in the majority of the operations. Patients who did not wish to conceive were advised to use a hormonal treatment (progestins, oral contraceptives, or levonorgestrel intrauterine system). Five patients were lost to follow-up, and the remaining 50 patients were followed for a mean duration of 97.5 months (range 5–315 months). During the follow-up period, 18 patients wished to become pregnant, and 13 (72.2%) had a successful delivery; nine (69.2%) of the pregnancies were in patients who had stage I or II endometriosis. It is not clear whether some of these pregnancies were following fertility treatment. Eleven patients developed infertility, six of these (54.5%) delivered a child, and two of these were following in vitro fertilization (IVF) treatment.

With this limited information we have, we can advise teenagers with endometriosis or their parents that while there will be an increased risk of infertility, the

majority of them will be able to become pregnant and have families. Some may need help to become pregnant, including IVF treatment. The likelihood of a successful outcome is probably higher in adolescents with minimal and mild endometriosis.

Impact of Surgery

Surgical treatment of endometriosis is known to be beneficial for fertility in women with a history of infertility. There is good evidence from randomized controlled trials indicating that surgery for minimal and mild endometriosis increases chances of spontaneous pregnancy in infertile women. Data from case series suggest that surgery also improves chances of pregnancy in women with moderate and severe endometriosis [5]. Fertility-sparing surgery is of value specifically in adolescents with endometriosis. However, evidence of a long-term benefit of surgery is lacking in women who have not tried for pregnancy yet. This point is particularly applicable to the adolescents. Possibility of a long-term benefit on fertility cannot be ruled out, and prospective long-term data collection is needed to answer this question.

Endometriosis is considered as a potentially chronic condition with a significant risk of recurrence, even after complete surgical treatment. Recurrence of endometriosis or its symptoms is a particularly difficult problem as the adolescents have many years ahead of them with potential risk of recurrence before they become menopausal [6]. Recurrence leads to repeat surgery in a significant proportion of patients; 10–47% of patients required repeat laparoscopy in published case series of adolescent endometriosis [3, 7–9]. Symptom recurrence is even more common; in the series by Tandoi et al. [8], 57% experienced recurrent pain during a 5-year follow-up, and only 23% had resolution or significant improvement of pain in the series by Audebert et al. [3]. Theoretically, surgery, particularly repeat surgery, can cause detrimental effects on future fertility by a number of ways:

1. Adhesions: Endometriosis itself causes adhesions. Adhesions between the ovaries and the ovarian fossa are seen even in early stages. Surgical treatment aims to separate adhesions and free up pelvic organs. However, adhesions frequently reform, and furthermore, de novo adhesion formation may occur. Control arm of a small randomized trial showed adhesions at second-look laparoscopy in 75% of women after laparoscopic surgery for endometriosis [10]. Although the use of antiadhesion agents may reduce risk of adhesion formation, the published studies are relatively small, and hence, there is uncertainty about their efficacy.
2. Reduction in ovarian reserve: There is now considerable amount of data indicating that ovarian reserve is diminished after endometrioma surgery depending on the type of endometrioma and technique used [11–13]. The effect is greater in women with bilateral endometriomas. This may not have an impact on the future chances of natural fertility, or at least there is currently no evidence that it does, but there is evidence that endometrioma surgery makes future IVF treatment

more difficult without improving the chances of success [14]. The detrimental impact of endometrioma surgery may be enhanced further by repeat surgery; hence, there is bigger concern in situations that require repeat surgery for endometriomas.

In summary, while it is impossible to rule out possibility of a benefit of early surgery for endometriosis in adolescence, long-term benefit on fertility has not been demonstrated. On the contrary, there is a theoretical possibility that surgery may have a potential detrimental impact due to postsurgical adhesions and reduced ovarian reserve. For these reasons, it is impossible to make a clear recommendation on the place of surgery to enhance future fertility in adolescents with endometriosis with the current available data.

Medical Treatment and Future Fertility

Medical treatment with hormones is known to be effective in the treatment of pain associated with endometriosis, but the current evidence clearly confirms that it does not improve fertility in infertile women [15]. Currently available data do not indicate a future fertility benefit either. Hormonal treatments, particularly those that suppress ovulation, are recommended to reduce risk of recurrence, particularly after endometrioma surgery. Although hormonal treatments are not beneficial for the management of functional ovarian cysts compared to expectant management, this secondary prevention approach using medical treatment is frequently used in the published literature on adolescent endometriosis and is likely to be beneficial for future fertility indirectly by reducing recurrences [16–18].

Adolescent Endometriosis and Fertility Preservation

Women with endometriosis may represent a suitable group for fertility preservation as they are at risk of reduced ovarian reserve due to detrimental impact of endometrioma surgery and potential harm of presence of endometrioma itself. This may be particularly the case for women with bilateral endometriomas and those who have recurrent endometrioma in the contralateral ovary after surgery [19]. For this reason, international recommendations suggest informing women of this possible option [20]. Adolescents are of a particular group of interest due to their greater risk of recurrence, lower likelihood of seeking pregnancy in the short to medium term, and higher expectation of success with the stored oocytes/ovarian tissue [19]. However, this group is also more likely to retain ovarian reserve better, compared to older women, after surgical treatment; hence, avoidance of delaying the pregnancy issue may be a better approach than fertility preservation. Currently, there is no overall consensus on the issue of fertility preservation in the adolescents.

Conclusions

There is limited data on the impact of endometriosis and its treatment on fertility in adolescents with endometriosis. Counselling teenagers with endometriosis and their parents can be based on scarce information in the published literature, but assumptions based on data from older women are frequently needed. Adolescents will need to be informed that their risk of infertility is increased, but the majority of them will be able to have children. Likelihood of pregnancy is probably higher in adolescents with minimal and mild endometriosis. Long-term benefit of surgical treatment on fertility is not known, but such benefit cannot be ruled out. Repeat surgery can potentially be detrimental to fertility or future fertility treatment due to adhesions and reduced ovarian reserve. Medical treatment that suppresses ovulation is likely to be beneficial, particularly after surgical treatment due to a reduction in recurrent endometriomas.

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Chapter 21
Fertility Outcomes – Reducing Ovarian Damage During Endometriosis Surgery

Roy Mashiach, Dahlia Admon, and Shlomo Mashiach

The Pathophysiology of the Decrease in Ovarian Reserve

The origin of ovarian endometriomas is unknown; however, it is generally believed that they initially result from progressive invagination (folding inwards) of an endometriosis nodule located on the ovarian surface [7]. In accordance with this theory, an endometrioma would be considered a pseudocyst, the wall of which is the inverted ovarian cortex. Hence, the removal of this cyst wall might involve removal of normal ovarian tissue with possible reduction of ovarian reserve and adverse implications for future fertility. Histological studies confirm that follicles are inadvertently removed by the stripping of the cyst wall. In a study by Muzzi et al. [8], the ovarian tissue removed along with the endometrioma wall mostly consisted of tissue which contained primary and secondary follicles (in 69% of cases).

Proper Surgical Technique for Excision of Endometrioma

Excision of an endometrioma cyst wall with minimal ovarian damage is often a complex exercise dependent on finding the plane of attachment of the fibrotic endometrioma to the ovarian cortex [7, 9, 10]. Meticulous surgical technique for the

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excision of the pseudo-capsule of ovarian endometrioma is necessary, geared toward finding the correct cleavage plane while achieving adequate hemostasis with the minimal use of coagulation and employing an energy device is important for preserving the ovarian reserve. Reich and Abrao [11] described their view of the proper technique of ovarian cystectomy: "The surgeon first identifies the site of rupture occurring during dissection of the ovary from the pelvic sidewall. In this opening, the fibrotic endometrioma is firmly attached to the ovarian cortex. Gentle peeling or needle vaporization of this junction with cutting current delineates the plane. A little concentrated work here goes a long way as, once started, the endometrioma cyst wall will usually peel easily from the ovarian parenchyma with traction. In many cases, the dissection is very close to the utero-ovarian ligament, whose vasculature is very susceptible to avulsion injury requiring bipolar electrosurgical application for hemostasis. Be very careful in this area. Excising the fibrotic pelvic sidewall and/or uterosacral ligament lesions to which the ovary was attached will reduce recurrences. Healthy ovarian tissue adjacent to the endometrioma cyst wall per pathology report indicates that the surgeon should try to improve **technique** the next time."

Nezhat et al. use the following technique for endometriomas over 2 cm [12]: "The cyst is punctured with the 5 mm trocar and aspirated with the suction-irrigation probe. Using high pressure irrigation, the cyst is irrigated, causing it to expand, and it is aspirated several times. This procedure allows examination of the cyst wall. After the repeated expansion and shrinkage with irrigation and suction, the cyst wall should separate from the surrounding ovarian stroma. If it does not, 5–20 ml of dilute vasopressin is injected between the stroma and the cyst wall. The cyst wall is removed by grasping the base with laparoscopic forceps at the puncture site. Pulling the two forceps apart and cutting between the structures creates a cleavage plane. Use of the laser or electro-surgery minimized bleeding because the blood vessels supplying the endometrioma are usually small enough to be cut and coagulated simultaneously. Another method involves hydro dissection of the plane between the cyst wall and the ovarian stoma. If the entire cyst cannot be separated from the ovary, the adherent sections are ablated or coagulated."

Ablation

Ablation of the endometrioma involves the opening and drainage of the endometrioma, or fenestration, followed by the destruction of the cyst wall using either electrosurgical current, cutting or coagulating current, or a form of laser or plasma jet energy. The recurrence rate of ovarian endometrioma following CO_2 laser ablation is higher than after excision. In a study by Vercellini et al. (a meta-analysis) [13], endometrioma recurrence was observed in 39 of 212 (18.4%) women treated with coagulation or laser vaporization and in 19 of 295 (6.4%) who underwent excision.

Evidence of Ovarian Damage

Assessing ovarian damage is quite challenging since ovarian reserve assessment is difficult [14]. Although various ovarian reserve tests have been applied widely, the debate continues over the ability of the tests currently available to indeed predict ovarian reserve [14]. Ovarian reserve tests include biochemical tests and ultrasonographic measurements of the ovary. Biochemical tests can be further divided into static measurements (in this chapter, we will discuss day 3 FSH levels and AMH levels) and provocative tests, such as the clomiphene citrate challenge test or the response to gonadotrophins. Anti-Mullerian hormone (AMH) is a glycoprotein hormone produced by small (primary, pre-antral, and antral) ovarian follicles and therefore directly measures the follicular pool. Serum levels of FSH, a pituitary hormone which is balanced by negative feedback from the ovary, in the early luteal phase, indirectly measure the ovarian reserve. Ultrasonographic measurements of ovarian reserve include antral follicle count (AFC) and ovarian volume. The AFC describes the total number of follicles measuring 2–10 millimeters in diameter that are observed during the early follicular phase. This parameter has been found to correlate with the follicular pool and the number of oocytes retrieved following stimulation.

The AFC is an accurate marker of ovarian reserve as the AFC is capable of demonstrating the effect of ovarian cystectomy on the operated ovary itself and therefore directly indicates the ovarian reserve expressed by each single ovary. As AMH expresses the ovarian reserve of both ovaries, a normal result may be the average of both ovaries, with a healthy ovary compensating for a reduced ovarian reserve in the contralateral affected ovary.

The endometrioma itself does not alter the ovarian function. In a study of 244 women with unilateral endometriomas (55% with left endometriomas and 45% with right endometriomas) monitored for ovulation over 1199 cycles, ovulation occurred at similar rates frowm the normal ovary and the endometriotic ovary (49.7% versus 50.3%) [15]. Although the endometrioma may reduce the number of follicles recruited in the ovary by exogenous FSH stimulation, there is no evidence that the cyst itself has an effect on pregnancy or live birth rates [16, 17].

Use of CO_2 laser appears to be advantageous. Less reduction in serum AMH concentrations and antral follicle count (AFC) was observed when vaporizing internal cyst walls using a CO_2 laser as the source of energy compared with excision of the cyst wall. The assumption is that CO_2 laser could vaporize only the filmy superficial internal lining up to 1.0–1.5 mm of the cyst wall [18] and therefore cause less thermal damage.

Ovarian surgery to remove the endometrioma has been shown to reduce the ovarian reserve as assessed by AMH levels; however, this effect has not been supported by measurement of the AFC [4, 19, 20]. A meta-analysis of eight studies of endometrioma cystectomy reported 38% lower AMH levels in women after ovarian cystectomy, compared with the levels measured prior to cystectomy [21].

Ovarian cystectomy for bilateral endometriomas may result in a greater reduction in AMH levels than unilateral ovarian cystectomy [22, 23]. It is unclear whether AMH levels fall as a result of direct surgical trauma to the ovary or due to the removal of normal ovarian tissue and follicles. A prospective study assessing ovarian function reported a greater loss of ovarian tissue and antral follicles in the women undergoing repeat surgery compared with women undergoing primary endometrioma resection [24]. The authors cautioned against repeat surgical intervention for endometriomas.

Women whose ovaries have been subjected to excisional surgery have been shown to display poorer responses to gonadotrophin stimulation for in vitro fertilization (IVF) [19–21]. Higher rates of premature ovarian failure [22] and a younger age at menopause [23] have also been reported after excision of bilateral ovarian endometriomas. Women whose ovaries have been subjected to excisional surgery have been shown to display poorer responses to gonadotrophin stimulation for in vitro fertilization (IVF) [25–27]. Higher rates of premature ovarian failure [28] and a younger age at menopause [29] have also been reported after excision of bilateral ovarian endometriomas.

Ozaki et al. [23] investigated, in a prospective study, the factors associated with diminished ovarian reserve, and the potential risk of becoming a poor ovarian responder before and after laparoscopic cystectomy of ovarian endometriomas. They aimed to evaluate the feasibility of presurgical prediction of postsurgical decreased ovarian reserve (DOR). For symptomatic ovarian endometrioma with a cyst >4 cm in diameter, 143 patients underwent laparoscopic cystectomy. The patients were divided according to the presurgical ovarian reserve (estimated using serum AMH levels) into two groups: (1) presurgical DOR (31 (21.7%) patients with AMH level <1.1 ng/ml) and (2) normal group (112 (78.3%) patients with AMH level <1.1 ng/ml).

Presurgical serum AMH concentrations and bilateral cystectomy were significant factors influencing the likelihood of a patient having postsurgical DOR at 3 and 6 months after surgery. The cumulative spontaneous pregnancy rate was significantly lower in the postsurgical DOR group at 6 months after surgery than in the postsurgical non-DOR group. Because the presurgical AMH concentrations significantly contributed to the likelihood of a patient having postsurgical DOR at 3 and 6 months after surgery, as assessed by logistic regression analysis, they investigated the optimal cutoff points of the presurgical AMH concentration using ROC curves to predict postsurgical DOR due to ovarian cystectomy. At 3 months after surgery, the optimal cutoff points of the presurgical AMH concentrations of the patients who underwent unilateral cystectomy and those who underwent bilateral cystectomy were 2.1 ng/mL [AUC, 0.83 (95% CI, 0.68–0.97); sensitivity 92.2%, specificity 76.9%; $p = 0.001$] and 3.0 ng/mL [AUC, 0.72 (95% CI, 0.57–0.87); sensitivity 69.6%, specificity 76.0%; $p = 0.01$], respectively, and at 6 months after surgery, the respective optimal cutoff points were 2.1 ng/mL [AUC, 0.85 (95% CI, 0.73–0.97); sensitivity 89.8%, specificity 73.3%; $p < 0.001$;] and 3.5 ng/mL [AUC, 0.80 (95% CI, 0.67–0.93); sensitivity 68.0%, specificity 91.3%; $p < 0.001$].

Muzzi et al. [20] performed a meta-analysis to assess the effect of surgery of an endometrioma on ovarian reserve as evaluated by AFC. They included all articles

reporting complete surgical excision of the endometrioma as well as articles reporting alternative surgical techniques, such as vaporization or coagulation of the cyst wall or a combination of the above. Non-excisional techniques were pooled separately from excisional techniques in the meta-analysis. Studies were excluded in the case of surgery for the recurrence of endometriomas. Thirteen studies were included. A total of 511 patients were included. No significant change in the mean AFC was observed before and after surgical excision of the endometrioma (mean difference 0.10, with 95% CI 21.45 to 1.65; P ¼ 0.90). Also, for non-excisional techniques, no significant change in the mean AFC was observed after surgery (mean difference 1.62, with 95% CI 23.78 to 7.03; P ¼ 0.56). Mean AFC for the ovary operated with excisional techniques was significantly less than the contralateral ovary (mean difference 21.40, with 95% CI 22.27 to 20.52; $P < 0.002$).

New Methods for Reducing Ovarian Damage During Endometriosis Surgery

Plasma Jet Ablation

In 2011, Roman et al. [30] described the use of plasma energy in order to ablate ovarian endometriomas: "The procedure for ablation using plasma energy starts in the same way as cystectomy. The origin of the cyst invagination is identified after lysis of the adhesions between the ovary and the adjacent broad ligament, leading to the characteristic 'chocolate fluid' evacuating from the cyst. In the few cases where major ovarian adhesions are not found, the invagination site is located on the antimesenteric part of the ovary, and the cyst is directly opened. Once the cyst is free from adhesions, the surgeon attempts to turn it completely inside out via the site of its original invagination of diameter averaging 1–2 cm (Fig. 21.1). Ablation of the

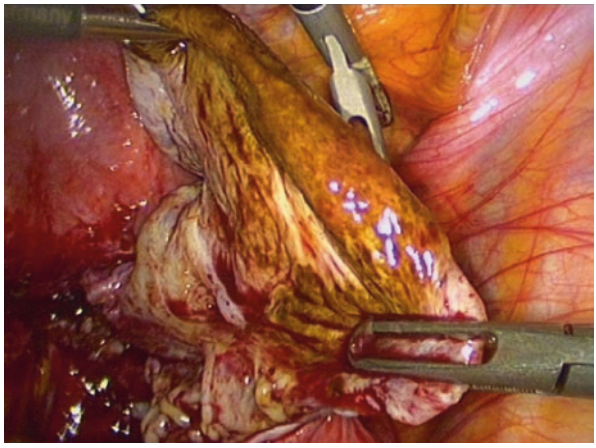

Fig. 21.1 Turning the ovary inside out. (Source: Roman et al. [30])

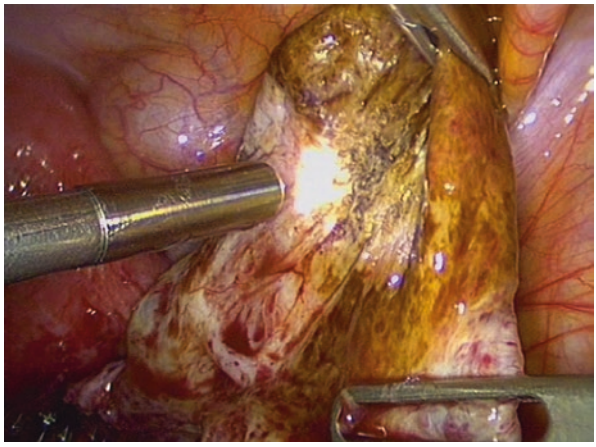

Fig. 21.2 Plasma jet ablation of the ovary. (Source: Roman et al. [30])

inner surface of the cyst is then performed using plasma energy in coagulation mode set at 40, at a distance averaging 5 mm from the tip of the handpiece, and with an exposure time limited to 1–2 seconds on each site (Fig. 21.2). Care is taken not to leave any untreated sites and to ablate the edges of the invagination site and the corresponding peritoneal implants on the adjacent broad ligament. When cyst reversion is not feasible, the surgeon progressively exposes the cyst interior to guide the plasma beam at an angle perpendicular to the inner surface of the cyst."

Initial results were encouraging: 15 patients treated by this technique were retrospectively compared to 15 patients who underwent cystectomy in their institute at the same time. Ovarian volume and AFC were studied. Women operated by cystectomy showed a statistically significant reduction in ovarian volume ($P < 0.001$) and AFC ($P < 0.001$) when compared with those operated on with ablation using plasma energy. Multivariate analysis showed that the relationship between the decrease in ovarian parameters and the use of the cystectomy technique remained statistically significant after adjustment for age, previous pregnancy, and cyst diameter.

In 2016, a French multicenter case-controlled study [31] aimed to compare postoperative pregnancy rate in infertile women with ovarian endometriomas larger than 3 cm in diameter, managed by either ablation using plasma energy or by cystectomy. One hundred and four patients were included. Endometrioma ablation using plasma energy was performed in 64 patients (61.5%) and cystectomy in 40 patients (38.5%). Patients managed by plasma energy were significantly older than those managed by cystectomy, had significantly higher overall revised American Fertility Society (rAFS) score, and had a higher rate of Douglas pouch obliteration, deep endometriosis, and colorectal localizations. Postoperative pregnancy rates were comparable after management of ovarian endometrioma by either ablation using plasma energy or cystectomy despite an overall higher rate of unfavorable fertility predictive factors in the women managed by ablation.

The Excision-Ablation Combined Technique

Donnez et al. [32] reported that the ovarian volume and AFC did not significantly differ between the operated ovary and the contralateral unaffected ovary, when combining excision and vaporization using CO_2 laser.

In brief, their method comprises of three steps: First, the endometrial cyst is opened and washed out with irrigation fluid. After identifying the plane of cleavage between the cyst wall and the ovarian tissue, the inner lining of the cyst is stripped from the normal ovarian tissue. If the excision provokes bleeding or the plane of cleavage is not clearly visible, the cystectomy is stopped. Thus, when approaching the hilus, where the plane of cleavage is less visible, resection of the dissected tissue (partial cystectomy) is performed. They estimated that the stripping technique allows removal of 80–90% of the cyst. After this first step (partial cystectomy), CO_2 laser is used to vaporize the remaining part of the endometrioma close to the hilus. They advise meticulous vaporization of all residual cyst wall to avoid recurrence. At the end of the procedure, the ovary is not sutured. Figure 21.3 shows the steps in detail. In this study, the operation was rapid. The maximum duration of surgery was 20 minutes per ovary. No intraoperative bleeding was encountered. Histological analysis revealed ovarian follicles in the removed specimen in only one case (2%).

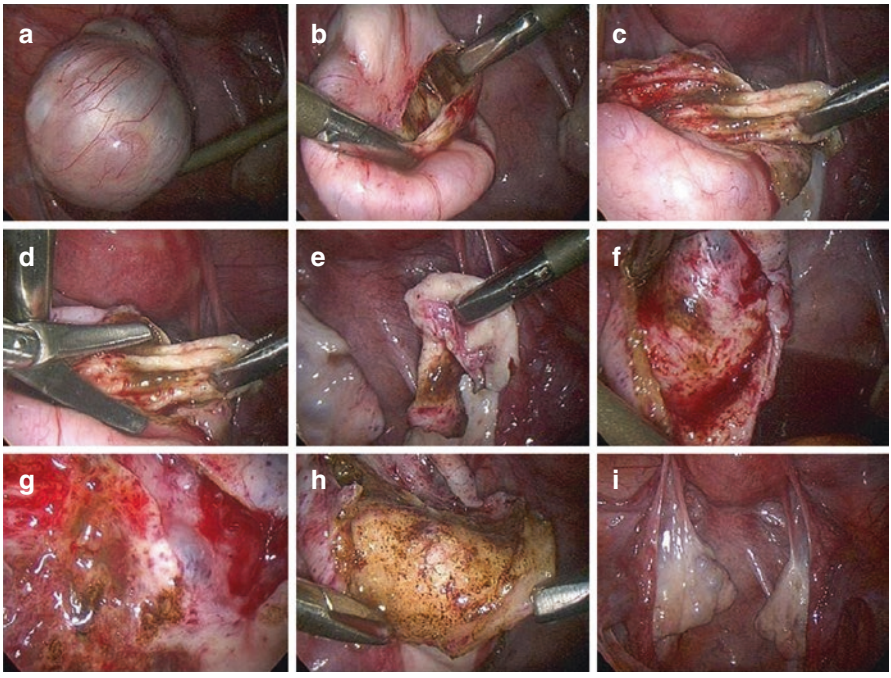

Fig. 21.3 The Donnez combined method. (**a**) The ovary before surgery. (**b**) The endometrial cyst is opened and washed out with irrigation fluid. (**c**) The inner lining of the cyst is stripped from the normal ovarian tissue. (**d**) Resection of the dissected tissue. (**e–g**) Donnez method; excisoin and vaporization of endometrioma. (**h**) CO_2 laser is used to vaporize the remaining part of the endometrioma. (**i**) The ovary after surgery. (Source: Donnez et al. [32])

Six months after surgery, the ovarian volume of the operated ovary and the AFC during the early follicular phase were $7.64 \pm 2.95\ cm^3$ and $6.1 \pm 3.2\ cm^3$, respectively.

Among the 20 women with unilateral endometriomas, ovarian volume and AFC were similar in the operated ovary and in the contralateral non-operated ovary.

In the series of 52 women, 37 wished to become pregnant. The pregnancy rate was 41% after 8 months. The recurrence rate at 6 months was 2%.

Ovarian Hemostatic Suturing

Bipolar coagulation of the ovary during or after ovarian endometrioma cystectomy further reduces ovarian reserve. Two studies compared ovarian reserve between laparoscopic ovarian cystectomy and open laparotomy with hemostatic suturing, and both indicated a significant decrease in ovarian reserve in the bipolar group as compared to the open suture group [33, 34]. This difference is not due to laparoscopy or laparotomy route of surgery, but it is related to the technique of hemostasis. Advancement of surgical technique and the spread of surgical competence and availability of proper instrumentation (e.g., barbed sutures) have made it possible to suture ovaries for hemostasis rather than using bipolar coagulation.

Peters et al. have reviewed 12 studies comparing suturing to bipolar hemostasis with a total of 1133 subjects [35]. They found suturing to be better than bipolar coagulation: Most (62.5%) of the studies demonstrated improved conservation of preoperative AMH levels in the suturing group, whereas the remainder did not see any difference when compared with the bipolar coagulation group. Seven of 12 studies investigated the impact of hemostasis using suture versus surgical energy during ovarian cystectomy, by means of AFC, and demonstrated a similar trend to AMH, albeit not as strongly. They concluded that "suturing is less damaging to the ovary when compared with other forms of surgical energy, including bipolar or ultrasonic cautery."

Summary

Excision of endometrioma should be considered in patients suffering from infertility. The key argument against surgery is the decrease in the ovarian reserve after surgery.

Surgeons must take all possible measures to reduce ovarian damage during surgery.

Surgical excision is the method of choice due to its lower recurrence rate when compared to other techniques. Meticulous surgical approach includes proper cleavage plane selection and minimal ovarian coagulation. The role of innovative methods to preserve ovarian function, such as plasma jet, and the role of ovarian suturing are promising and should be studied further.

The possibility of a reduced ovarian reserve should be discussed with the patient, but this issue should not change the well-defined indications to surgery, especially when the evidence supporting damage to the ovarian reserve is inconclusive or inconsistent.

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Chapter 22
Fertility Preservation in Adolescents with Endometriosis

Daniel S. Seidman

Abbreviations

AFC	Antral follicle count
AMH	Anti-Müllerian hormone
FPT	Fertility preservation techniques
IVM	In vitro maturation
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
POF	Premature ovarian failure
TS	Turner syndrome

Introduction

It is well recognized that women with endometriosis may suffer from an accelerated decrease in their ovarian reserve [1–4]. This decline in the number of follicles in the ovaries may be further compromised by ovarian surgery for the treatment of endometriosis, especially following the removal of endometriomas [5, 6]. Obviously when endometriosis is diagnosed at a very early age, concern must be raised regarding future fertility. Comprehensive prospective data is not yet available regarding the risk for infertility in women diagnosed with endometriosis as adolescents, but there is evident reason for worry.

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New technologies for long-term fertility preservation have lately been shown to be effective and are now offered to women from a very early age [7, 8]. These fertility preservation options include new techniques, like ovarian tissue freezing, that may be more suitable than oocyte or embryo cryopreservation for young girls [9–12]. While most of these fertility preservation techniques (FPT) were developed for women with serious diseases, mainly cancer, there is growing recognition that they may be invaluable for women with nonmalignant disease that can have severe adverse effect on fertility and specifically endometriosis [13–17].

Ovarian Reserve and Endometriosis

Women diagnosed with endometriosis have been shown to be at risk for lasting damage to their ovarian reserve [15] (Table 22.1). The exact mechanisms leading to the progressive loss of follicle reservoir in some women with endometriosis is still subject to ongoing debate [26]. The detrimental effects of endometriosis may have several mechanisms, including direct and indirect cytotoxic effects on follicular recruitment in the ovarian cortex [2, 4, 5]. Moreover, the long-recognized adverse effect on future fertility may clearly present a bigger challenge once endometriosis is diagnosed in a very young age [12, 27, 28].

It has not yet been fully determined to what extent, if at all, does extraovarian endometriosis and its surgical management adversely affect ovarian reserve. The extent of surgery-related decline in ovarian reserve is hard to predict based on

Table 22.1 Ovarian reserve in women with and without endometrioma

Authors	Endometriosis (no. of patients)	Controls (no. of patients)	*P* value
AMH			
Shebl [18]	2.57 ± 2.0 (153 pt)	3.46 ± 2.30 (306 pt)	<0.001
Hwu [19]	2.34 ± 0.19 (141 pt)	3.31 ± 0.08 (1.323 pt)	<0.001
Ercan [20]	1.62 ± 1.09 (43 pt)	2.06 ± 0.51 (17 pt)	NS
Uncu [1]	2.81 mean (30 pt)	4.20 (30 pt)	0.02
AFC	Affected ovary	Contralateral ovary	
Almog [21]	7.5 ± 0.7 (53 pt)	9.3 ± 0.9 (53 pt)	<0.05
Biacchiardi [22]	3.3 ± 3.2 (43 pt)	8.4 ± 6.0 (43 pt)	<0.0001
COH results	Pt with endometriomas	Control group	
	(no eggs retrieved)	(no eggs retrieved)	
Suzuki [23]	4.40 ± 2.99 (80 cycles)	5.34 ± 2.99 (283 cycles)	0.0037
Kumbak [24]	13.9(5–33) (85 pt)	16.4 (5–37) (83 pt)	0.03
Opøien [25]	8 ± 5.3 (350 pt)	9.2 ± 5.6 (1.171 pt)	<0.01

Adapted from Carrillo et al. [15]

preoperative or perioperative factors. Bipolar cauterization of the ovary seems to be associated with the extent of ovarian damage [5]. It may thus be prudent to assess the ovarian reserve preoperatively and delay or avoid surgical excision as far as is possible if subsequent fertility is a concern [15].

Ovarian Reserve Assessment

Endometriosis and its surgical treatment can affect ovarian reserve (Table 22.2). The optimal biomarker of ovarian reserve estimation in women with endometriosis is still under examination. Both serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) are widely used today as biomarkers of ovarian reserve. However, serum levels of AMH seem at present to offer the most reliable quantitative marker of ovarian reserve. The AFC may be a less reliable marker for ovarian reserve in adolescents, especially in the presence of an endometrioma in the ovary or following recent use of oral contraceptive pills.

A recent meta-analysis concluded that AMH seems to be a more appropriate biomarker of ovarian reserve than AFC in cases with endometrioma [34]. As discussed below, it has been repeatedly reported that women with endometrioma have decreased serum AMH levels as compared with healthy controls and patients with other benign ovarian cysts [4, 35] (Table 22.1). AMH levels are even lower after surgical excision, and the decline seems permanent [16] (Table 22.2).

Endometrioma

Ovarian endometrioma is a frequent manifestation of endometriosis in women of reproductive age. The impact of ovarian endometrioma per se on ovarian reserve is still controversial and the effect of ovarian surgery is still actively discussed [35–37] (Table 22.2). It has not yet been fully elucidated whether the endometrioma-related decline in ovarian reserve is progressive in nature and whether it exceeds the surgery-related decline. There is also no agreement on the effect of endometrioma bilaterality on ovarian reserve [36, 37].

Ovarian endometriomas are not rare in young women, and a high recurrence rate following surgery has been described in adolescence [28]. The presence of ovarian endometrioma per se may impair ovarian reserve and alter ovarian functional anatomy [34]. Kasapoglu et al. [38] performed a prospective longitudinal study in 40 women to evaluate whether the presence of an endometrioma on the ovary is associated with a progressive decline in ovarian reserve and to compare the rate of decline with natural decline in ovarian reserve. They found that women with endometrioma experienced a progressive decline in serum AMH levels, which was faster than that in healthy women [38]. It was further shown that both the presence and excision of

Table 22.2 Markers of ovarian reserve prior and post ovarian surgery

Authors	No. Pt (time)	AMH (ng/ml)		AFC[a]		FSH (mIU/ml)		Ovarian volume[a]	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
Biacchiardi [22]	43 (9mo)	3.0 ± 0.4	1.3 ± 0.3 $P < 0.0001$	3.3 ± 3.2	5.1 ± 3.6 NS	6.6 ± 2.0	8.0 ± 3.7 NS	10.5 ± 0.8	8.6 ± 0.9 $P < 0.0001$
Tsolakidis [29]	10 [1] (6mo)	3.9 ± 0.4	2.9 ± 0.2 $P = 0.026$	2 ± 1	2.4 ± 08 NS	7.2 ± 0.8	16.6 ± 3.8 NS	89.7 ± 29.6	11.5 ± 4.8 NS
Tsolakidis [29]	10 [2] (6mo)	4.5 ± 0.4	3.99 ± 0.6 NS	1.3 ± 0.5	4.36 ± 0.8 $P < 0.02$	7.7 ± 0.8	11.0 ± 2.9 NS	7.7 ± 23.6	11.0 ± 2.9 NS
Celik [30]	65 (6mo)	1.78 ± 1.71	0.72 ± 0.79 $P < 0.001$	4.9 ± 2.2	6.4 ± 2.2 $P < 0.008$	6.37 ± 3.04	6.67 ± 4.53 NS	–	–
Hirokawa [31]	38 (1mo)	3.9 ± 2.5	2.1 ± 1.6 $P < 0.001$	–	–	–	–	–	–
Var [32]	48 [1]	–	–	5.58 ± 1.13	3.67 ± 1.26 $P < 0.001$	–	–	13.03 ± 1.13	6.27 ± 1.95 $P < 0.01$
Var [32]	48 [3]	–	–	5.42 ± 0.77	4.75 ± 0.6 $P < 0.02$			13.56 ± 1.5	9.87 ± 2.01 $P < 0.01$
Kwon [33]	100 (3mo)	4.97 ± 2.83	3.33 ± 2.08						
Uncu [1]	60 (6mo)	4.2 ± 2.3	1.8 ± 1.3 $P = 0.02$	14.7 ± 4.1	10.4 ± 4.2 $P = 0.63$				

Adapted and updated from Carrillo et al. [15]

[a]Affected ovary. [1]Laparoscopic cystectomy. [2]Three-step procedure. [3]Coagulation

endometriomas can apparently lead to a significant decrease in serum AMH levels, which is sustained for at least 6 months after surgery [1] (Table 22.2).

Busacca et al. [6] reported on a series of 126 patients who underwent laparoscopic excision of bilateral endometriomas. They found that three women suffered from postsurgical ovarian failure. Thus, a low but definite and very disturbing risk of premature ovarian failure exists immediately after surgery [6]. The detrimental effect of surgically removing ovarian endometriomas, and especially bilateral endometriomas, has been subject or concern for some time [34]. Damage to the ovarian tissue by surgical intervention to remove ovarian endometriomas has been attributed to a number of mechanisms [15] (Fig. 22.1). Surgical technique may also influence the amount of damage to the ovarian cortex. For instance, it has been suggested that laparoscopic excision (cystectomy) should be preferred for endometriomas over laparoscopic ablation (drainage and coagulation) to preserve fertility [3].

Uncu et al. [1] tried to assess whether the presence of endometriomas and their laparoscopic excision can lead to a decrease in ovarian reserve. The possible adverse effect on the ovarian follicles was determined by measuring serum AMH levels. The authors found that both the presence and excision of endometriomas may have a negative effect on serum AMH levels. The adverse effect persisted for at least 6 months after surgery [1]. While these findings were mostly in agreement

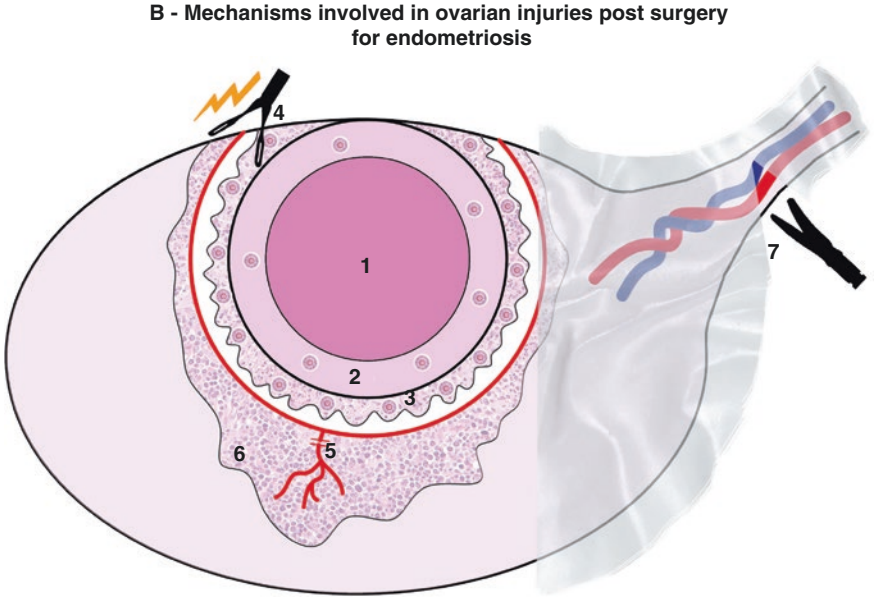

Fig. 22.1 The causes of follicle loss during surgery for endometriosis involve injury to blood vessels and stroma and removal of healthy cortex. 1. Endometrioma; 2. pseudocapsule of the endometrioma; 3. healthy cortex containing significant number of follicles stripped with pseudocapsule; 4. coagulation of vascular bed; 5. blood vessels injuries; 6. edema/inflammation; 7. adhesiolysis and subsequent injuries of the bloody vessels. (With permission from Carrillo et al. [15])

with previous studies, Uncu et al. [1, 5] were among the first to show that the presence of endometrioma per se is associated with a decrease in ovarian reserve (Table 22.1).

Younis et al. [34] recently performed a systematic review and meta-analysis to study the impact of unilateral versus bilateral ovarian endometrioma on ovarian reserve biomarkers before and after endometrioma cystectomy. They analyzed each of the unilateral and bilateral groups separately and showed a significant and sustained serum AMH drop by 39.5% and 57.0%, respectively, from baseline to after the operation. They concluded that their results challenge the concept that endometrioma per se adversely affects ovarian reserve, whereas endometrioma cystectomy, especially as bilateral operation, has a deleterious and sustained effect on ovarian reserve [34]. Santulli et al. [36] similarly concluded that the presence of an ovarian endometrioma is not associated with presentation for infertility. However, ovarian surgery was clearly associated with a demonstratable decline in AMH. They further suggested that since low AMH implies a shorter reproductive life span, excision of endometrioma should be cautiously considered, especially in bilateral cases [36].

Preventing Damage to the Ovarian Reserve

It is a common supposition these days that adolescent endometriosis is a progressive disease [39]. Thus, adolescents with endometriosis may be exposed over many years to the potentially cytotoxic effects of ovarian and extraovarian endometriotic lesions. It was recently suggested that some of this damage to the ovaries could be prevented through new nonsurgical therapeutic modalities [37]. For instance, free radical production could be blocked by antioxidants and the autophagic process by increasing apoptosis [37]. Moreover, the progesterone receptor ratio could be restored by using progestin or progesterone receptor modulators and decreasing local estrogen production through the use of an aromatase inhibitor [37]. In addition, apparently, metalloproteinases and relaxin activity, as well as the inflammatory process, may be controlled. Many of these pharmacological treatments lend themselves to local administration and can be applied through intracystic drug administration. It was also proposed that endometrial growth in the endometrioma could be suppressed by intracystic application of synthetic progestins, such as levonorgestrel or danazol, and by applying selective progesterone receptor modulators, such as mifepristone, ulipristal, or asoprisnil, without affecting ovarian activity [37].

Beyond medical and surgical intervention, to prevent injury to the ovarian reserve, adolescents with endometriosis should be encouraged to choose healthy behavioral and lifestyle choices, like abstaining from smoking and avoiding excess body weight, as this may also contribute to the preservation of future fertility [39, 40].

Fertility Preservation Technologies

The use of fertility preservation technologies (FPT) has become widely accepted as a standard of care for women at an increased risk of acute premature ovarian failure (POF), most commonly due to the urgent need for cancer treatment [7, 10]. The idea of offering FPT to adolescent women with endometriosis stems, as described above, from our growing understanding that endometriosis and related surgery may compromise ovarian reserve [4, 5]. Moreover, it is now recognized that when young women undergo laparoscopy for diagnosis and treatment of endometriosis, this may present a unique opportunity to offer ovarian cortex tissue sampling and freezing [9, 15]. While still considered an experimental procedure in most countries, ovarian tissue cryopreservation and transplantation have been increasingly applied worldwide to restore fertility in patients with malignant and nonmalignant pathologies with risk of premature ovarian insufficiency. It has yielded more than 130 live births up to now, and almost all transplanted patients recovered their ovarian function [41].

Currently, FPT is being offered to a growing number of prepubertal and adolescent girls that are at risk of compromised fertility due not only to gonadotoxic treatments but also to repeat ovarian surgery or genetic disorders [42]. An example for such a genetic disorder that presents concern is Turner syndrome (TS) where young girls and adolescents are at high risk of gonadal dysgenesis and premature ovarian insufficiency. A growing number of young girls with TS are therefore being offered FPT [43–45]. A recent study found that cryopreservation of oocytes or ovarian tissue was performed experimentally in over 150 girls and adolescents with TS over the last 16 years [45]. The authors concluded that the efficacy of fertility preservation options in females with TS is still unknown due to the lack of follow-up data. At this time, it must be noted that no births have yet resulted from freeze-thawing of prepubertal ovarian cortex, although the results of this approach in adults are encouraging [43]. The long-term efficacy of FPT in females with TS is still unknown. However, these preliminary results seem to support the concept that cryopreservation of ovarian cortex offers a valid option to preserve fertility in these young girls at risk of POF [43, 44]. It is apparent that the efficacy, feasibility, and risks of ovarian cryopreservation in children must be further assessed in order to validate the technique. Moreover, in the event of spontaneous menarche, TS adolescents should be referred for counselling regarding FPT during the transition to adulthood to prevent referral delay and time-related reduced ovarian reserve [45].

Oocytes Cryopreservation

The most commonly used FPT is cryopreservation of oocytes [46]. This technique has been shown to be successful for fertility preservation in both elective and oncologic indications [47]. Elizur et al. [13] were the first to report on cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis. They

suggested that egg freezing in patients with severe endometriosis could be a new indication for fertility preservation. However, egg freezing demands the use of ovulation induction hormonal treatment and the use of transvaginal oocyte aspiration. Thus, despite the proven efficacy of oocyte cryopreservation, the use of this FPT may be less relevant for premenarche and nonsexually active young adolescents. It was thus suggested that immature oocytes could be collected from very young girls without hormonal stimulation and then matured in vitro and vitrified.

Retrieval of immature oocytes from unstimulated ovaries, followed by in vitro maturation (IVM), was initially proposed to avoid the risks and side effects of exogenous gonadotropin administration [48]. Therefore, during the past decades, IVM was mainly offered to patients with polycystic ovary syndrome (PCOS) at high risk of ovarian hyperstimulation syndrome (OHSS). However, the development of fertility preservation has recently opened new perspectives in the field of IVM. It was therefore suggested that new indications for IVM may now include fertility preservation before endometrioma excision [48]. Yet, the quality of in vitro matured oocytes obtained from patients with endometriosis remains to be objectively established.

It is clear that the feasibility of performing IVM in young adolescents depends on the genetic quality of the oocytes obtained, as well as our ability to mature the oocytes in the lab. A recent research paper published in *Science* [49] followed chromosome segregation in human oocytes from females aged 9 to 43 years and showed that aneuploidy follows a U-curve. Thus, it was found that young girls, like advanced aged women, may have a higher incidence of detrimental aneuploidy. Moreover, Gruhn et al. [49] demonstrated that specific segregation error types show different age dependencies, providing a quantitative explanation for the age and aneuploidy U-curve association. Interestingly, they found that whole-chromosome nondisjunction events are preferentially associated with increased aneuploidy in young girls, whereas centromeric and more extensive cohesion loss limit fertility as women age [49].

In vitro maturation was shown to be possible in fully grown germinal vesicle (GV) oocytes obtained from small antral follicles, retrieved directly from human ovarian tissue without exogenous gonadotrophin stimulation. Cryopreservation of immature oocytes may therefore offer a form of FPT suitable for young adolescents and girls [50].

Karavania et al. [51] evaluated the efficacy of IVM and oocyte retrieval rates after ovarian tissue cryopreservation in young premenarche girls facing chemo- and radiotherapy. They found that IVM performed after ovarian tissue cryopreservation in premenarche girls and specifically in very young girls (4 years and younger) yields substantially decreased maturation rates compared with postmenarche patients. This observation raises a question as to the utility of current IVM technique in this age group. Patrizio and Albertini [52] also noted concern regarding the utilization of IVM in young girls and emphasized that, as was previously recognized from animal studies, the oocyte-follicle unit undergoes a critical series of changes during the pubertal transition required for the acquisition of meiotic and developmental competencies.

Not all authorities support the claim that oocytes obtained from prepubertal ovarian tissue of very young patients are incapable of IVM as some teams have reported successful cryopreservation of in vitro matured oocytes for fertility preservation in pediatric females [8]. However, others still claim that oocytes harvested from prepubertal ovaries are deficient in their ability to initiate and complete the process of oocyte maturation, a status often referred to as meiotic competence [27]. Karavania et al. [51] also reported that while the harvesting of oocytes is comparable over a wide age range, the ability of isolated oocytes to undergo IVM is limited in younger patients.

Ovarian Tissue Cryopreservation

Follicle-containing ovarian tissue can be obtained for fertility preservation from pediatric patients, including prepubertal girls [52, 53]. Cryostorage of ovarian cortical tissue with the potential for reimplantation later in life therefore seems at present to be the only practical fertility preservation option currently available for prepubertal girls [9–12] (Table 22.3).

Surgical treatment of endometriosis can reduce the number of follicles/oocytes, and this effect may be more severe in adolescents in need for bilateral ovarian surgery. Therefore, freezing of ovarian tissue seems best suited for adolescents as the ovarian cortex in young women is highly rich in primordial follicles [9].

Obtaining ovarian cortical tissue usually involves one-sided surgical removal of ovarian cortical tissue or complete oophorectomy [10]. The harvested cortical

Table 22.3 Ovarian reserve in women with and without endometrioma

Authors	Endometriosis (no. of patients)	Controls (no. of patients)	*P* value
AMH			
Shebl [43]	2.57 ± 2.0 (153 pt)	3.46 ± 2.30 (306 pt)	<0.001
Hwu [11]	2.34 ± 0.19 (141 pt)	3.31 ± 0.08 (1.323 pt)	<0.001
Ercan [44]	1.62 ± 1.09 (43 pt)	2.06 ± 0.51 (17 pt)	NS
Uncu [45]	2.81 mean (30 pt)	4.20 (30 pt)	0.02
AFC			
Authors	Affected ovary	Contralateral ovary	*P* value
Almog [46]	7.5 ± 0.7 (53 pt)	9.3 ± 0.9 (53 pt)	<0.05
Biacchiardi [36]	3.3 ± 3.2 (43 pt)	8.4 ± 6.0 (43 pt)	<0.0001
COH results			
Authors	Pt with endometriomas (no eggs retrieved)	Control group (no eggs retrieved)	*P* value
Suzuki [47]	4.40 ± 2.99 (80 cycles)	5.34 ± 2.99 (283 cycles)	0.0037
Kumbak [13]	13.9(5–33) (85 pt)	16.4 (5–37) (83 pt)	0.03
Opøien [48]	8 ± 5.3 (350 pt)	9.2 ± 5.6 (1.171 pt)	<0.01

Adapted from Carrillo et al. [15]

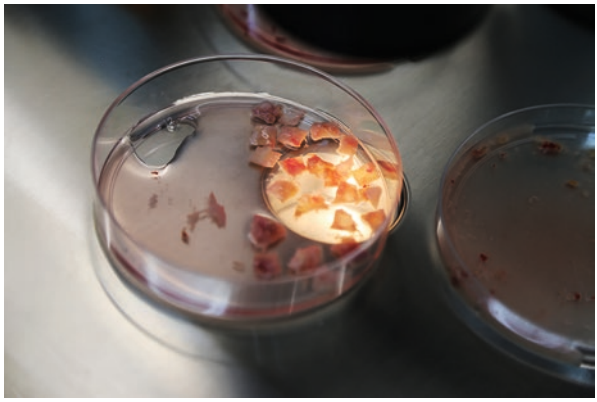

Fig. 22.2 Piece of cortical ovarian tissue obtained for long-term cryopreservation. (With permission from Prof. Dror Meirow)

tissue is dissected into thin (1–2 mm) strips measuring 0.5 × 1 cm^2, which are frozen for future transplantation (Fig. 22.2). Primordial follicles are located in a poorly vascular environment and are relatively resistant to ischemia. This allows the survival of follicles during the immediate posttransplantation ischemic period and may result in successful reestablishment of fertility [54]. In cases of endometriosis, cortical tissue can be harvested and stored, thereby sparing the follicles from a potential future disease progression that could occur in the ovary left in situ [15]. Laparoscopic tissue harvesting may be technically more difficult in cases of severe pelvic adhesions. Moreover, removing healthy cortical tissue in young girls may further deteriorate their compromised ovarian reserve. However, during surgical removal of endometrioma, healthy fragments of ovarian cortex can be isolated and cryopreserved with little additional risk of damage to the ovarian tissue.

The source of cortical tissue stored might originate from healthy cortical tissue attached to the capsule, which has been removed during the surgery and of cortical fragments that are loosely attached to the ovary at the end of dissection [15]. Ovarian cortical tissue collection can be performed at any center operating for endometriosis as there is no need for patients' referral since the ovarian tissue can be safely transported prior to freezing to fertility preservation center [55].

Data available from oncological patients who underwent ovarian tissue reimplantation shows more than 90% endocrine restoration rate and high pregnancy rate, either spontaneous or following IVF [41]. Yet the quantity and quality of follicles, as well as reproductive potential of cortical tissue that was attached adjacent to the endometrioma wall, should be further studied [15]. For patients with endometriosis undergoing surgery, consultation on ovarian tissue storing should be individualized according to patients' age, ovarian reserve status, presence of bilateral ovarian lesions, and expectations for repeated surgery. While in some cases healthy cortical tissue is removed unintentionally as a by-product on endometrioma excision, a deliberate removal of normal cortical tissue is far less straightforward and

should be viewed as a potential threat for ovarian reserve. Adolescents and their family members should be carefully consulted regarding the indication for such intervention in light of its potential risks and benefits, as well as the limited clinical experience.

Autotransplantation of ovarian tissue has yielded to date 130 live births, including one from tissue that was cryostored in early adolescence [8, 41]. The idea of offering fertility preservation in young girls with severe endometriosis is receiving growing recognition and is advocated by some experts as a legitimate part of routine care [15, 17, 48]. When young women undergo laparoscopy for diagnosis and treatment of endometriosis, they should be alerted to the reality that this may present a unique opportunity to offer ovarian cortical tissue sampling and freezing as fertility preservation measure [42].

Proper assessment of the risk of ovarian failure, existing ovarian reserve, and patient choice have to be taken into account for the amount of the ovarian tissue needs to be retrieved [53, 54]. Microsurgical principles need to be adopted to reduce the risk of graft's damage and compromising ovarian function [54]. Ultimately, ovarian tissue cryopreservation could be applied not only as an FPT but also as an option to recover complete ovarian function in teenager patients with premature ovarian insufficiency and to postpone menopause by providing ovarian tissue-based hormone replacement therapy.

Conclusions

The predicted future availability of noninvasive diagnostic testing, genetic or hormonal, for endometriosis may increase the early diagnosis of endometriosis among adolescents with or without dysmenorrhea. This is likely to lead to a growing need to educate adolescents and their caregivers regarding methods to preserve their future fertility. Adolescents with severe endometriosis may be at significant risk for ovarian tissue damage, which may lead to infertility and rarely to premature ovarian failure. The risk for a compromised ovarian reserve is especially high in adolescents who require repeated surgical intervention and in the presence of bilateral endometriomas. Adolescents with severe endometriosis and those likely to undergo ovarian surgical intervention should be consulted regarding the current available fertility preservation techniques (FPT) (Table 22.4). Adolescents are good candidates for ovarian tissue freezing. This procedure can be undertaken as part of the surgery planned to treat endometriosis or to remove ovarian endometriomas. Oocyte cryopreservation may also be offered to some of the postmenarche girls. The use of cryopreservation of in vitro matured oocytes in young premenarche girls is a less supported option for FPT in adolescents suffering from endometriosis. Personalized counseling should be offered to all adolescents with endometriosis taking into account age, extent of ovarian involvement, current ovarian reserve, and previous

Table 22.4 Fertility preservation techniques for adolescents with endometriosis—pro and cons

Pro	Cons
Embryo/oocyte cryopreservation	
Documented results especially when embryos are frozen	Risk of infections related to oocyte retrieval and abscess formation
No risk of procedure-related ovarian reserve depletion	Concern regarding meiotic competence
The pick-up may avoid contact of the oocyte with the detrimental effect of the peritoneal fluid	Need of ovarian stimulation that might cause the progression of the disease (controversial data)
Need for repeated IVF cycles in order to collect an adequate number of oocytes that can be stored	
Ovarian tissue cryopreservation	
No vaginal procedure and no need of ovarian stimulation	
Effective technique for fertility preservation	Laparoscopic procedure in these patients may be more difficult and riskier
Easily performed during the surgical intervention for the disease	Storing tissue surrounding cyst or pseudocapsule—number and quality of follicles are questionable
	Storing healthy tissue remote from cyst may result in ovarian damage and reduced ovarian reserve
Frozen tissue is spared from potential destruction in cases of disease recurrence	No results, so far, have been shown in adolescents with endometriosis

Adapted from Carrillo et al. [15]

and impending surgeries for endometriosis, along with current success rates and possible risks associated with FPT.

Conflict of Interest Statement There are no conflicts of interest or industrial affiliations.

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Part VIII
Endometriosis Comorbidities

Chapter 23
Comorbidities in Adolescent Women with Endometriosis

Rebecca L. Surrey and Eric S. Surrey

The overall objective of this chapter is to discuss comorbidities of endometriosis in adolescence, which may differ from those experienced by adults with this disease. Some comorbidities are universal and not age-specific, but there appears to be a unique symptomatology faced by the adolescent population which can significantly impact their quality of life.

Endometriosis in Adolescents

Endometriosis is a complicated disease that affects approximately 10% of the general female population [1]. Associated symptoms clearly impact patient quality of life in many ways, by the burden of disease itself, and because of its comorbidities. These connections are especially not well understood among the adolescent population.

Although symptoms often present when patients are less than 20 years old, on average, women do not receive a diagnosis until they are in their early 30s [2–4]. This long delay means that, for some patients, the majority of adolescence involves experiencing and managing symptoms and comorbidities without access to timely diagnosis and appropriate treatment. Patients often express frustration because their complaints are not taken seriously or can be misdiagnosed during visits to multiple specialists [4–6] (Fig. 23.1). It can take years to formally diagnose endometriosis, which adds especially to the psychosocial impact of the disease.

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Fig. 23.1 Sequelae of misdiagnosing comorbidities of endometriosis. Adolescent patients can present with a variety of complaints pertaining to their endometriosis comorbidities. If the health-care practitioner does not have these high on their differential, the patient could be referred unnecessarily to a specialist and/or undergo extraneous workup, delaying appropriate management

It is also often unclear what symptomatology adolescents may present with beyond dysmenorrhea, pelvic pain, and the other expected symptoms of endometriosis as this age group is not well studied. While there are no standardized screening guidelines, women's and adolescent health-care providers should be aware of possible comorbidities and appropriate assessment or management recommendations.

Universal Comorbidities

It can be difficult to categorize symptoms patients experience as direct effects of endometriotic implants as opposed to disease comorbidities or other coexisting conditions. Assuming the most common symptoms associated with endometriosis are dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and infertility, the host of other associated symptoms can be considered comorbidities.

Some of these comorbidities are reported among women of any age with endometriosis, including adolescents. Gastrointestinal disturbances reminiscent of irritable bowel syndrome are common. Patients may complain of nausea, bloating, constipation, or diarrhea, among others. Patients may also suffer urinary tract disturbances, such as bladder or flank pain, urgency, or nocturia [4, 5].

Patients with endometriosis experience an increased incidence of mood disturbances, such as low mood, hopelessness, and depression. Fourquet et al. noted that of women with self-reported surgically diagnosed endometriosis, 27% described low energy and 35% felt depressed or discouraged [7]. All of these symptoms and comorbidities together significantly affect usual daily functioning and can contribute to an increased amount of absenteeism (hours of missed work) and presenteeism (impairment in performing work tasks) [5, 8, 9]. On average, endometriosis patients lose approximately 1 day's worth of work time per week as a result of their symptoms [7]. One small study of women aged 17 to 53 years old reported more than 75% of survey responders stated that endometriosis interferes with their life "a lot" or "very much," the most extreme options [5].

Finally, it is important to keep in mind, women with endometriosis potentially have a higher risk of breast cancer, some ovarian cancers such as endometrioid or clear cell and melanoma, although this has not been universally confirmed [2, 10].

Unique Comorbidities in Adolescents

In addition to the previously described comorbidities that affect women of all ages with endometriosis, adolescents suffer unique additional challenges (Table 23.1).

Combined oral contraceptives (COCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are the typical initial treatment choices for pelvic pain; however, refractory pain can be a significant problem. In a systematic review of women aged 10–21 years, 75% of those with chronic pelvic pain resistant to COCs or NSAIDs ultimately had laparoscopic evidence of endometriosis [15]. It is important, therefore, to keep endometriosis high on the differential for adolescent patients with uncontrolled pelvic pain, particularly when not responsive to these first-line interventions.

Additionally, two studies looking at immune disease patterns occurring alongside endometriosis found an increased incidence of fibromyalgia, a disorder characterized by widespread and often migratory musculoskeletal pain. A study by Sinaii et al. that did not stratify women by age described a significantly increased incidence of fibromyalgia in those with endometriosis compared to those without (5.9% vs. 3.4%, respectively, $p < 0.0001$). Palmor et al. reported similar outcomes in a more recently published trial that specifically focused on adolescents and young adults with laparoscopically confirmed endometriosis. They too found that this population was significantly more likely to have a diagnosis of fibromyalgia than controls (OR 5.48, 95% CI 1.13–26.59) [11, 12]. Along with pain throughout the body, patients with fibromyalgia also experience fatigue and difficulty sleeping, among other things which all can negatively affect quality of life.

Table 23.1 Comorbidities associated with endometriosis

Body system	Comorbidities
Psychiatric	Low mood, depression, increased substance use, impaired quality of life [3, 5, 7, 8]
Pulmonary	Increased prevalence of asthma [11, 12]
Gastrointestinal	Nausea, bloating, cramping, diarrhea, dyschezia, rectal pain [2, 4, 13, 14]
Urinary	Bladder or flank pain, dysuria, nocturia [4, 5, 15]
Infectious disease	Increased prevalence of allergies [11, 12]
Rheumatology	Increased incidence of fibromyalgia [11, 12, 15]

Adolescents with endometriosis also experience increasing degrees of substance use and abuse. This is often due to insufficient management of chronic pain with extended use of ineffective first-line treatments but may also represent a form self-medication as a psychological coping mechanism [5, 13]. It is critical to screen for substance use in this population during each clinic visit. There are multiple validated screening and assessment tools specifically for adolescents available to the clinician as recommended by the National Institute on Drug Abuse, including the Brief Screener for Tobacco, Alcohol, and other Drugs (BSTAD) or the Drug Abuse Screen Test (DAST-20) [16].

Adolescents with endometriosis also report an increased incidence of gastrointestinal symptoms such as nausea, dyschezia, constipation, intestinal cramps, or rectal pain. These can contribute to patients missing partial or whole school days or extracurricular activities. This constellation of GI complaints may also result in patients being referred to a gastroenterologist, where vague symptoms may be misdiagnosed with and unsuccessfully treated for disease processes such as irritable bowel syndrome (IBS), resulting in further delay in obtaining appropriate diagnosis and treatment [2, 4, 13, 14].

Patients with endometriosis are more likely to have allergies and asthma. Sinaii et al. noted that of women with a diagnosis of endometriosis, 12% reported that they had asthma and 61% had allergies [11]. Palmor et al. again reported similar results, demonstrating that adolescents with endometriosis had a significantly high likelihood of reporting comorbid asthma (OR 1.66, 95% CI: 1.12–2.45) or allergies (OR: 1.7, 95% CI: 1.21–2.41) [12]. Patients should be queried about respiratory symptoms at rest or with exercise, as well as any history of rash, hives, or other allergic-type reactions. These are issues that can often be easily managed if they are appropriately identified.

There is inconsistent data regarding associations between endometriosis and other autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, psoriasis, or eczema. Some studies report a correlation among the overall endometriosis population; however, the manuscript by Palmor et al. focusing on adolescents reported no significant association. This requires further appropriately designed investigation [2, 11, 12].

All of these abovementioned comorbidities, as well as symptoms directly attributable to the disease itself, combine to significantly affect quality of life. In a study by Moradi and coworkers, patients aged 16–24 years reported the biggest impact endometriosis had on their lives was on their education because they had to take time off school, had difficulty focusing, or felt less productive [5]. They were concerned about school absenteeism (hours missed from school) or presenteeism (impairment of ability to perform school tasks) due to their symptoms [5, 12, 17]. In fact, adult women with deep endometriosis are more likely to report having a history of absenteeism from school in adolescence [14]. Being distracted during school because of the need to deal with symptoms of the disease and its comorbidities, or actually having to take time away from classes or schoolwork, can negatively impact educational performance and have a cyclical effect on psychosocial stress.

Another study surveyed patients aged 15–19 years about their experience with endometriosis, and respondents described their concern with a disrupted adolescence, including a "struggle to be normal" [6]. Their social life is affected because they often miss out on school functions. They often *express or* express concerns more typically attributed to adults such as worrying about future fertility or health insurance. They report frustration in not understanding their disease or feeling like they are not getting sufficient care in a timely manner by their health-care providers [5, 6]. Patients should be specifically asked about how their endometriosis and comorbidity symptoms affect their ability to function in school or during extracurricular activities. Counselling or other resources should be made available as appropriate.

Conclusion

A challenge to managing comorbidities associated with endometriosis in adolescents is a lack of appropriately designed research trials. Many studies only include patients as young as 17 or 18 years of age and adults. Even a recently updated committee opinion on adolescent dysmenorrhea and endometriosis from the American College of Obstetricians and Gynecologists (ACOG) barely mentions comorbidities [17]. This dearth of data results in an unclear picture of the incidence of comorbidities in adolescents and the true extent of their effect on quality of life. Fewer physicians are trained in treating this disease and its sequelae particularly in this population of younger women, which, along with limited research as guidance, can lead to a hesitance to offer appropriate surgical or advanced medical intervention.

There are some general recommendations available for management and resources for both health-care practitioners and patients (see Table 23.2), but there are no clear or consensus guidelines for treating endometriosis or for screening for its comorbidities [14]. Regardless, it is important to remember the majority of adult women eventually diagnosed with endometriosis report their symptoms began in adolescence. Complaints in younger populations must be taken seriously [2, 3, 5]. While an adolescent patient's gastrointestinal disturbances may actually be due to IBS, or their refractory back pain may actually be an orthopedic issue, it is crucial that health-care practitioners do not immediately jump to the easy conclusion. Perform a thorough history, including an extensive review of systems, and complete physical exam along with appropriate imaging studies during clinic visits for young patients with pelvic pain and clinically suspected endometriosis, particularly those with refractory symptoms.

Table 23.2 Resources for health-care practitioners and patients

Endometriosis Association: Endometriosis Resources for Teens
ACOG Committee Opinion Number 760. Dysmenorrhea and endometriosis in the adolescent. Dec 2018.

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Part IX
Associated Pathology

Chapter 24
Thyroid Disorders in Adolescence

Esra Karslioglu-French and Pushpa Viswanathan

Hypothyroidism

Hypothyroidism can be classified as primary when the defect lies in the thyroid gland itself, central when it is due to pituitary dysfunction (referred to as secondary hypothyroidism), or hypothalamic dysfunction (referred to as tertiary hypothyroidism) (Table 24.1).

Causes of Hypothyroidism

Congenital hypothyroidism (CH) is common in newborns occurring in about 1 in 2000 newborns [1]. It is due to either defects in thyroid gland development (dysgenesis) or failure of an anatomically normal gland with the synthesis or secretion of thyroid hormones (dyshormonogenesis). Other causes include placental transfer of maternal-blocking antibodies and other exogenous and environmental etiologies including iodine deficiency. After the implementation of universal newborn screening, children with CH are detected early, and devastating neurodevelopmental delays are prevented. Iodine deficiency is one of the most common causes of primary acquired hypothyroidism worldwide, but incidence has decreased with widespread iodization of salt.

Autoimmune hypothyroidism (AH), due to Hashimoto thyroiditis, is the most common cause of acquired hypothyroidism in children, adolescents, and adults. The prevalence of AH in childhood is an estimated 1% to 2% with a 4:1 female predominance [2]. Incidence of acquired hypothyroidism, most frequently due to Hashimoto/

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Table 24.1 Etiology of hypothyroidism

Primary: 1. Thyroiditis: autoimmune, subacute thyroiditis, infectious 2. Congenital hypothyroidism: dysgenesis, dyshormonogenesis, hypothyroidism due to maternal transfer of blocking antibodies 3. Status post thyroidectomy/radioiodine ablation for Grave's disease or thyroid cancer 4. Medications and supplements: lithium, amiodarone, tyrosine kinase inhibitors, interferon alpha, CTLA-4 blocking antibody, excess iodide intake (kelp, supplements, radiocontrast dyes), antithyroid meds, intentional or inadvertent ingestion of thyroid hormones
Secondary: 1. Pituitary tumors, pituitary destruction (infection, postpartum, surgery, compression from locally invasive tumors), trauma, postpartum pituitary necrosis, infiltrates into pituitary from other systemic illnesses 2. Head and neck radiation, radiation for cancer treatments, in preparation for a bone marrow transplant 3. Medications (retinoid X receptor ligand) and supplements 4. Genetic: septo-optic dysplasia syndromes (POU1F1, PROP1, LHX3, HESX1, OTX2), mutations in gene coding for TSH-beta subunit 5. Transient central hypothyroidism from severe non-thyroidal illness
Tertiary: Hypothalamic dysfunction
Peripheral resistance to the action of thyroid hormone: Mutations in thyroid hormone receptor genes *THRB* and *THRA*

Table 24.2 Interpretation of thyroid labs

TSH	Free T4[a]	T3	Interpretation
High	Normal	Normal	Subclinical hypothyroidism
High	Low	Low/ normal	Hypothyroidism
Low/normal	Low	Low/ normal	Secondary/central hypothyroidism
Low	High	High/ normal	Hyperthyroidism
"Inappropriately" normal/high normal	High	High	Resistance to thyroid hormone+
Low/normal	Low	Low	Euthyroid sick syndrome/non-thyroidal illness

+Obtain proper medication history, and repeat labs in 1–2 weeks using different assay. If inappropriate, TSH is persistent.

[a]Free T4 levels preferred to T4 as TBG concentration can affect T4 level. r/o TSH-secreting pituitary adenoma (TSH-alpha subunit which will be elevated in TSH-secreting adenomas, MRI)

chronic lymphocytic thyroiditis, increases during school age and adolescence. Family history is often positive for autoimmune thyroid disease. The diagnosis of AH is confirmed by measurement of a high thyroid-stimulating hormone/thyrotropin (TSH) level and low thyroxine (T4) level (Table 24.2). Ninety percent have positive antithyroid peroxidase antibody (TPO Ab), and 20–50% have antithyroglobulin antibodies (TgAb). Other causes of thyroiditis besides autoimmunity include

certain infections, which cause transient hypothyroidism (Table 24.1). Numerous medications can also cause hypothyroidism including lithium, amiodarone, and antiepileptics. Relatively newer medications including tyrosine kinase inhibitors and interferon-alpha used for hepatitis C viral infection induce or exacerbate the appearance of thyroiditis. During the last decade, cancer immunotherapy field has brought to light a series of immune-related adverse events including thyroiditis, which has been described, e.g., after the administration of monoclonal antibodies that block CTLA-4 [3] (Fig. 24.1).

Acquired hypothalamic or pituitary disorders can cause central hypothyroidism due to TRH and/or TSH deficiencies. Central hypothyroidism presents with a low T4 level and a non-elevated TSH level (Table 24.2).

Thyroid hormone resistance is a rare cause of either congenital or acquired hypothyroidism. This occurs when there is either resistance to thyroid hormone (RTH) or resistance to TSH. Patients with TSH resistance have inactivating mutations of the TSH receptor (TSHR) gene. Two forms of RTH are recognized: (1) generalized resistance to thyroid hormones and (2) selective pituitary resistance to thyroid hormones. Clinical manifestations such as mental retardation and delayed bone maturation have been described in individuals with generalized thyroid hormone resistance. Patients with partial TSH resistance are usually clinically euthyroid being able to compensate by increasing thyroid hormone levels. RTH is mostly due to mutations in the *THRB* gene. These patients have an "inappropriately" normal TSH level with a high free T4 and T3 levels (Tables 24.1 and 24.2). This pattern indicates defective feedback inhibition of the hypothalamic-pituitary-thyroid axis and impaired pituitary response to thyroid hormone. Despite high levels of thyroid hormone, tissues that express the mutant thyroid hormone receptors (TR), TR beta, i.e., pituitary and liver, are functionally hypothyroid. Tissues that primarily express TRα, such as the heart, show the effect of excess thyroid hormone, increased heart rate. Due to the tissue-specific expression of the different TR isoforms, manifestations include both of hypothyroidism (growth delay, hearing impairment) and hyperthyroidism (tachycardia and anxiety) [4]. Recently, dominant negative mutations in the *THRA* gene have been identified. Manifestations in these patients differ dramatically and characterized by severe growth and developmental retardation, low/normal TSH, low-normal T4, and high T3 levels [5].

Autoimmune Thyroid Diseases

Autoimmune disorders are a broad range of related diseases in which inappropriate immune responses of the body arise against its own cells, tissue, and organs, resulting in inflammation and damage. This response may affect only a particular tissue/organ of the body (such as in autoimmune thyroiditis) or may be systemic (such as systemic lupus erythematosus). A proper balance between pro-inflammatory and regulatory mechanisms is a requirement for sufficient tolerance of the body against its own cells. In autoimmunity, this is not maintained.

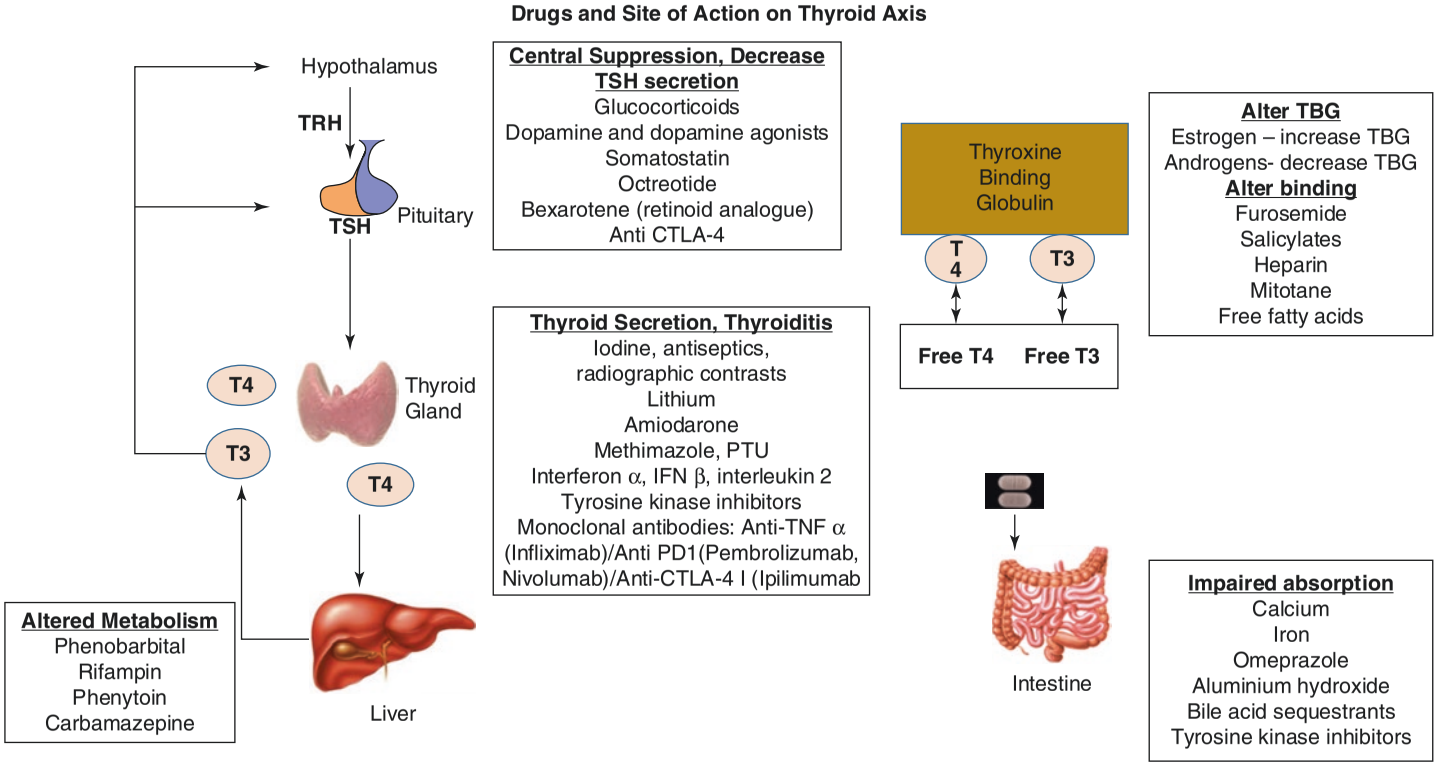

Fig. 24.1 Drugs that interact with thyroid function

Among autoimmune thyroid diseases (AITD), Hashimoto's thyroiditis (HT) and Graves' disease (GD) are prevalent. AITD is more common in females. Biological explanation for the gender difference is not clear. There are several hypotheses including skewed X chromosome inactivation [6].

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune thyroid disorder where there is lymphocytic infiltration of the thyroid gland followed by a gradual destruction and fibrous replacement of the thyroid parenchymal tissue. There is production of antithyroid antibodies, especially against thyroperoxidase (anti-TPO), antithyroglobulin (anti-Tg), and very rarely TSH receptor-blocking antibodies. The destruction and fibrous replacement of the follicle cells lead to hypothyroidism. HT is significantly more frequent in individuals suffering concurrently from other autoimmune diseases such as type 1 diabetes (T1D), rheumatoid arthritis, alopecia areata, celiac disease, etc. It is also more common in patients with trisomy 21 and Turner syndrome.

In GD, immune system produces TSH receptor antibodies that mimic action of TSH. Binding of ligand results in stimulation of adenyl cyclase and thyroid hormonogenesis and growth. TSH receptor antibodies in GD are further discussed in hyperthyroidism section.

Autoimmune diseases including hypothyroidism and Graves' disease have been found in slightly increased prevalence in women diagnosed with endometriosis in some studies, although not confirmed by others [7–10]. Endometriosis shares immunological features with autoimmune diseases including increased levels of cytokines, e.g., IL-6 and TNF-alpha, impaired apoptosis, and increased autoantibody formation [8]. While infertility in endometriosis patients is thought to be caused by altered pelvic anatomy, molecular mechanisms might be involved in this entity as well.

According to the current knowledge, in HT, a complex interaction between genetic and nongenetic factors presumably results in enhanced thyroid antigen presentation and reduced immune self-tolerance leading to autoimmune response mediated predominantly by Th1-type cytokines such as TNF-α, IFN-γ, and IL-2. This is followed by thyroid destruction by apoptotic pathways and clinical disease [11]. Several genes are reported to be associated with the disease occurrence, progression, and severity. Genes for human leukocyte antigen (HLA), cytotoxic T-lymphocyte antigen-4, protein tyrosine phosphatase nonreceptor-type 22(PTPN22), thyroglobulin, vitamin D receptor, and cytokines are considered to be of importance. TPOAb and TgAb both show high affinity for their respective antigens. Unlike TgAbs, TPOAbs can activate complement and are postulated to cause damage to thyroid cells due to antibody-dependent cell cytotoxicity [12]. Nevertheless, there is little evidence that both antibodies have a prime role in the pathogenesis of HT, and it is far more likely that both T-cell-mediated cytotoxicity and activation of apoptotic pathways influence the disease outcome. However, thyroid antibodies serve as a useful marker for the diagnosis of thyroid autoimmunity.

Among endogenous factors for the disease development, the attention is focused predominantly on female sex, pregnancy with postpartum period, and fetal microchimerism. Several nutritional/environmental factors have been implicated in the

development of autoimmune diseases including high iodine intake, selenium deficiency, certain drugs, and chemicals [13]. Studies have also suggested a role for other common micronutrients, most notably iron and vitamin D, and gut microbiota on HT risk [14]. Adequate iron status is essential for the production of thyroid hormones T3 and T4. HT is frequently associated with other autoimmune disorders. Indeed, a considerable proportion of HT patients have celiac disease [15] or autoimmune gastritis [16], and these comorbid conditions are regarded as the major cause of iron deficiency in HT patients. This also needs to be considered in iron deficiency anemia in adolescent girls with menorrhagia/endometriosis. Therefore, since autoimmune diseases coexist, a proper well-balanced diet needs to be emphasized.

The level of dietary iodine intake has a very significant effect on the pattern of thyroid disorders in populations. While iodine deficiency is recognized to have multiple adverse effects on the thyroid, with regard to autoimmune thyroiditis/HT, there is more evidence for an association with iodine excess, especially in genetically susceptible individuals [17]. To avoid an increased risk of HT, it is therefore important to ensure, as far as possible, that iodine intake falls within the relatively narrow range of the recommended levels (Table 24.3). On a population basis, this would be represented by a median urinary iodine concentration in adults of 100–200 μg/L. Authorities introducing iodine fortification of the food supply in a country (e.g., universal salt iodization) need to ensure that such fortification is introduced very cautiously. Recent trends for dietary supplements which is advertised for thyroid health also need to be carefully monitored.

In genetically susceptible individuals, several environmental factors may trigger thyroid autoimmunity by increasing the immunogenicity of thyroid autoantigens, enhancing antigen presentation in the thyroid, and reducing self-tolerance. Consequently, various pro-inflammatory cytokines are produced by immune and thyroid cells, resulting in predominantly Th1 and Th17 responses with an increased Th1/Th2 ratio. Meanwhile, increased production of pro-apoptotic cytokines leads to thyrocyte apoptosis and, finally, thyroid destruction [18]. In addition, a decreased number or impaired function of regulatory T cells (Tregs), which are pivotal for

Table 24.3 Recommended Dietary Allowances (RDAs) for iodine

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	110 mcg[a]	110 mcg[a]	–	–
7–12 months	130 mcg[a]	130 mcg[a]	–	–
1–3 years	90 mcg	90 mcg	–	–
4–8 years	90 mcg	90 mcg	–	–
9–13 years	120 mcg	120 mcg	–	–
14–18 years	150 mcg	150 mcg	220 mcg	290 mcg
19+ years	150 mcg	150 mcg	220 mcg	290 mcg

[a]Adequate intake: Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes. Washington, DC: National Academy Press, 2001

maintaining peripheral tolerance and suppressing excessive immune response, has been recognized to play an important role in the pathogenesis of HT [19].

Signs and Symptoms

Thyroid disorders are common especially in adolescent females. There is increased risk of thyroid nodules and thyroid cancer in adolescent females with HT. Careful history taking should include personal history of head and neck radiation, family history of thyroid disease, symptoms related to goiter, personal and family history of any autoimmune disease, family history of nodule or thyroid cancers, diet, and medication intake or any other over-the-counter supplement.

Typical features of hypothyroidism include dry skin, constipation, fatigue, cold intolerance, menstrual abnormalities, delayed relaxation phase of deep tendon reflexes, and muscle weakness. Reduced conversion of carotene to vitamin A and increased levels of carotene may give the skin a yellowish color. However, many of the signs and symptoms are absent in milder degrees of thyroid failure. A sharp deceleration in growth is frequently seen in children with acquired hypothyroidism. Contrary to common belief, hypothyroidism is rarely the etiology of weight gain. In fact, in children, excess weight gain (generally less than 10–20 lbs) is associated with mild elevations in TSH (between 5 and 10 mIU/L), with normalization of the TSH level after achieving weight loss [20]. An enlarged thyroid gland/goiter is the most common physical examination finding. Other examination findings include bradycardia, delayed reflexes, and myxedema of the face and extremities.

Attention to physical examination findings, combined with selected laboratory and radiologic tools, aids in the early diagnosis and treatment.

Laboratory Evaluation

For children with suspected hypothyroidism, TSH and T4 samples should be obtained. Triiodothyronine (T3) and reverse T3 levels are rarely helpful in the diagnosis of hypothyroidism and should not be obtained from the majority of patients. The levels of thyroid-binding proteins (thyroxine-binding globulin, transthyretin, and albumin) affect total T4 levels, so a free T4 level is generally a better measure of thyroid hormone status.

Children with primary hypothyroidism have a high level of TSH and a low level of T4. An elevated level of TSH and a normal level of T4 indicate subclinical hypothyroidism (Table 24.2). A significant percentage of patients with subclinical hypothyroidism convert to normal thyroid status with observation; however, the presence of a goiter and/or positive thyroid antibody levels, in particular TPOAb, is associated with an increased risk of progression to overt hypothyroidism (TSH level above 10 mIU/L) [21].

As noted above, biochemical markers of Hashimoto's thyroiditis are TPOAb and TgAb in the serum which are present with a higher prevalence in females than in males and increase with age.

Routine ultrasound is not recommended in autoimmune hypothyroidism unless asymmetry or nodules are palpated clinically.

Treatment

Treatment is usually hormone replacement using levothyroxine tablets (LTx). Recommendation is to take the tablets once daily, 15–30 minutes prior to food consumption, avoiding coadministration with calcium, iron, and soy products. LTx dosing is based on body surface area (100 μg/m2/d) or on age and weight following the general pattern:

- 1–3 years of age – 4–6 μg/kg/d
- 3–10 years of age – 3–5 μg/kg/d
- 10–16 years of age – 2–4 μg/kg/d
- 17 years of age or older – 1.6 μg/kg/d [21]

Additional TSH and free T4 samples should be obtained 6–8 weeks after initiating therapy. Once a therapeutic dose has been established, the clinician should check thyroid function every 4–6 months until the child achieves final height or every 6–8 weeks following a change in levothyroxine dose. The goals of treatment are to maintain clinical and biochemical euthyroidism and to ensure normal linear growth and development throughout childhood and adolescence.

Hyperthyroidism

Causes of Hyperthyroidism

Patients can have thyrotoxicosis secondary to (1) excess production and secretion of thyroid hormone, (2) release of preformed thyroid hormones from thyroid gland, and (3) exogenous thyroid hormone (Table 24.4).

More than 95% of cases of hyperthyroidism in children and adolescents are due to Graves' disease (GD) [22]. The incidence of GD peaks during adolescence. It occurs more frequently in females than in males like HT.

One study found a higher prevalence of GD among women with endometriosis compared to control group, possibly due to shared characteristic of these two disorders: autoimmunity. Additional studies are needed to confirm this finding and clinical significance [9].

Table 24.4 Etiology of hyperthyroidism in childhood and adolescence

Thyrotoxicosis due to hyperthyroidism (increased production of thyroid hormones)
Autoimmune hyperthyroidism
Graves' disease
Hashitoxicosis
Congenital non-autoimmune hyperthyroidism
Persistent sporadic congenital non-autoimmune hyperthyroidism (PSNAH)
Hereditary familial non-autoimmune autosomal-dominant hyperthyroidism
Autonomous functioning nodules
Toxic adenoma
Toxic multinodular goiter
McCune-Albright disease
TSH-induced hyperthyroidism
TSH-secreting pituitary tumors
Pituitary resistance to thyroid hormone
Tumors
Hydatiform mole, choriocarcinoma
Struma ovarii, teratoma
Transient thyrotoxicosis (excess release of preformed thyroid hormones)
Chronic lymphocytic thyroiditis
Subacute thyroiditis
Drug-induced thyroiditis
Drug-induced thyrotoxicosis
Thyroid hormone ingestion
Iodine-induced hyperthyroidism (iodine, radiocontrast, amiodarone)

In addition to etiologies listed in Table 24.4, TSH receptor activating mutations can cause congenital non-autoimmune hyperthyroidism. Familial hyperthyroidism due to gain-of-function mutations in the TSH receptor gene can mimic neonatal Graves' disease [23], whereas nonfamilial congenital hyperthyroidism due to gain-of-function mutations is identical to those found in thyroid adenomas and produces solitary or multiple hyperfunctioning adenomas [24].

Other rare causes of hyperthyroidism in childhood include TSH-producing pituitary adenomas, pituitary resistance to thyroid hormones, and ingestion of exogenous thyroid hormone or iodine.

Signs and Symptoms

Classic symptoms and signs include goiter, tachycardia, nervousness, tremor, increased appetite, weight loss, diarrhea, proximal muscle weakness, and heat intolerance. Puberty may be delayed. If menarche has occurred, secondary amenorrhea is common. GD is characterized clinically by thyromegaly, hyperthyroidism, and infiltrative ophthalmopathy. Severe ophthalmopathy is rare in childhood and occurs in less than 50% of children with GD. Pretibial myxedema and acropachy are not described in adolescents.

Laboratory Evaluation

In hyperthyroidism, plasma levels of T3 are often more elevated than those of T4, and TSH concentrations are suppressed. In the presence of pituitary TSH-secreting adenomas and pituitary resistance to thyroid hormone in addition to T3 and T4 levels, TSH is also elevated or inappropriately normal (Table 24.2).

GD diagnosis is confirmed by demonstration of disease-specific TSH receptor antibodies (TRAb). TRAb can be stimulating or blocking. Autoantibodies of the immunoglobulin G1 class bind to the extracellular domain of the TSH receptor (TSI) and stimulate follicular cell function and growth. Other autoantibodies to the TSH receptor (TBII) block thyroid cell function. Antibodies to the thyroperoxidase (TPO) and cytotoxic antibodies can also be detected in GD. Transplacental passage of TSI from mothers with GD causes neonatal autoimmune-mediated hyperthyroidism in their offspring. Teenage females need to be cautioned that TRAb levels may persist after definitive treatment and pose a risk to future pregnancies.

In GD, thyroid ultrasonography reveals the enlargement of the thyroid gland, with reduced, nonhomogeneous echogenicity and increased perfusion. In contrast to adults, thyroid scintigraphy is only required in atypical cases. If a patient has nodules detected by ultrasonography, scintigraphy is beneficial to rule out autonomous functioning nodules.

Treatment

Treatment options for hyperthyroidism include antithyroid medications, surgery, and radioiodine (RAI) treatment [25]. The treatment practices of GD in children show variation among institutions and health-care providers [26]. GD treatment needs to be individualized after discussion of advantages, disadvantages, and efficacy of each option with patient and parents.

Antithyroid drugs propylthiouracil (PTU) and methimazole (MMI) reduce hormone synthesis by inhibiting the oxidation and organic binding of thyroid iodide [27]. Both medications are associated with adverse events, but PTU use should be avoided in favor of MMI due to higher risk of severe liver injury. According to 2008 FDA report, the risk of PTU-induced liver failure leading to transplantation is 1 in 2000 children and adolescents [28]. In adults, this risk is estimated to be 1 in 10,000 individuals [29].

The typical MMI dose is 0.2–0.5 mg/kg per day, with a range from 0.1 to 1.0 mg/kg per day [22]. MMI has better safety profile compared to PTU but still associated with adverse events. MMI-related adverse events include agranulocytosis, urticaria, arthralgia, gastrointestinal problems, and rarely Stevens-Johnson syndrome and vasculitis. All patients that are prescribed MMI should be given instructions to stop medication and contact their physician should they develop unexplained fever and sore throat. In this circumstance, a white blood cell count should be obtained.

The duration of ATD in children before considering RAI is not clear. In children, when ATDs are used for 1–2 years, remission rates are generally 20–30% [30]. The presence of low TRAb levels and small thyroid gland suggests possibility of remission on medical therapy. Patients with high TRAb levels and large thyroid glands have lower rates of remission [31].

Clinicians usually offer MMI treatment for 1 or 2 years and proceed to surgery or RAI treatment. Long-term treatment with MMI is also an option as long as adverse events and progressive thyromegaly do not occur.

The goal of RAI treatment for GD is to induce hypothyroidism, which is achieved with high success rate of 95% [25]. ^{131}I doses are typically calculated to deliver the desired amount of radiation based on gland size and RAI uptake. Alternatively, some centers administer all patients the same fixed dose of ^{131}I. If patient is severely hyperthyroid, it is reasonable to use MMI until T4 levels normalize to prevent worsening of hyperthyroidism with ^{131}I [32]. Hypothyroidism usually develops 2–3 months posttreatment. If hyperthyroidism persists 6 months after therapy, retreatment is indicated.

If there is residual thyroid tissue in young children after RAI treatment, there is theoretical risk of thyroid cancer. If RAI therapy is chosen as treatment for GD in children, sufficient ^{131}I should be administered in a single dose to render the patient hypothyroid.

In addition to thyroid cancer risk, potential effect of RAI on other cancers is examined in several large cohorts of adults. These studies have not revealed increased cancer incidence or mortality [33]. Many physicians still remain concerned about the risks of carcinogenesis. Based on cancer risk projections from estimated whole-body, low-level radiation exposure as related to age, it is theoretically possible that there may be a low risk of malignancies in very young children treated with RAI. Thus, RAI therapy is avoided in very young children (<5 years) [34].

Surgery by an experienced thyroid surgeon is preferred in individuals with large thyroid glands (>80 g) when definitive treatment is needed as the response to RAI may be poor [35]. The acute complications following thyroidectomy include hypocalcemia, hematoma, and recurrent laryngeal nerve paresis. Long-term complications include hypoparathyroidism and recurrent laryngeal nerve injury. The complication rates are higher in children compared to adults. The complication rate for total thyroidectomy is lower when surgery is performed by a high-volume (>30 thyroidectomies per year) surgeon [36].

When Labs and Symptoms Do Not Match

Primary care providers often measure thyroid levels for a variety of complaints. When the lab results and symptoms do not match, interference with assay should be considered including heterophile antibodies. Some very common causes include estrogen containing pills and biotin. Combined hormonal pills (oral contraceptive pills containing estrogen) can elevate thyroid-binding globulin levels and create elevated T4 levels

with normal TSH. Free T4 levels will be normal. Usage of skin and hair products is very prevalent in adolescent females. Exceeding levels of biotin (>3000 ug) have been recognized to cause interference with assays measuring thyroid levels. Biotin can cause falsely high free T4, T3, and TRAb combined with falsely low TSH [37].

Impact of Thyroid Disorders on Growth and Puberty

Hypothyroidism causes poor linear growth and/or growth failure and, if undiagnosed, may compromise adult height. This is an extremely important point to monitor since growth spurt occurs in early adolescence in girls and late adolescence in boys. T4 and T3 are important regulators of somatic growth, metabolism, brain development, and other vital processes in developing and adult mammals [38].

Pubertal onset is regulated partly by a brain-dependent process, whereby increased pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) leads to the activation of pituitary-gonadal axis to awake the entire reproductive system. THs also facilitate proper development and function of the reproductive system [39, 40] . Children with severe hypothyroidism generally have delayed pubertal development. In rare occasions, they develop precocious puberty, which is described as Van Wyk-Grumbach syndrome [41]. However, the mechanism underlying how TH acts on the HPG axis has not been fully elucidated. There are several reports indicating the influence of abnormal thyroid status on pubertal disorders involving the two neuroendocrine systems, the hypothalamo-pituitary-thyroidal axis and the hypothalamo-pituitary-gonadal axis. Some studies indicate that increased TSH levels cause hyperprolactinemia and alter GnRH pulsatile secretion, which lead to delayed LH response, resulting in delayed puberty [42]. Other papers indicate that the increased TSH levels activate gonadal function by stimulating FSH receptor in gonads because the structure of FSH and thyrotropin receptors is similar, which is responsible for precocious puberty [43]. Recently, a hypothalamic neuropeptide, gonadotropin inhibitory hormone (GnIH) is reported to directly inhibit gonadotropin-releasing hormone (GnRh) neurons and gonadotropin synthesis and release in mammals including humans [44]. In contrast to GnIH, the product of Kiss1 gene, kisspeptin, is a potent stimulator of the hypothalamo-pituitary system to control puberty onset and normal reproductive performance in mammals. GnIH is also suggested to act as an inhibitory factor on kisspeptin neurons because a subset of kisspeptin neurons expresses GnIH receptors and receives GnIH fiber contact in mammals [45].

Thyroid Nodules and Thyroid Cancer

Thyroid Nodules

Nodules are common in this age group; up to 13% of older adolescents or young adults have thyroid nodules [46]. Iodine deficiency, prior radiation exposure, a history of preexisting thyroid disease, and several genetic syndromes are associated

with the development of thyroid nodules in children. Childhood cancer survivors who were treated for their primary malignancy with radiation therapy, especially survivors of Hodgkin lymphoma, leukemia, and central nervous system tumors, are at high risk [47].

Benign and malignant thyroid tumors can occur in patients with APC-associated polyposis, the Carney complex, the DICER1 syndrome, the PTEN hamartoma tumor syndrome, and Werner syndrome. Cases of differentiated thyroid cancer (DTC) have also been reported in Beckwith-Wiedemann syndrome, the familial paraganglioma syndromes, Li-Fraumeni syndrome, McCune-Albright syndrome, and Peutz-Jeghers syndrome [48]. Increased prevalence of thyroid nodules and cancer is reported in patients with autoimmune thyroiditis [49].

While identifying thyroid nodules that warrant FNA in children, ultrasound characteristics and clinical context should be used rather than nodule size alone. A size criterion is problematic in children because thyroid volume changes with age and the size of the nodule alone does not predict malignant histology [50, 51]. Diffusely infiltrative form of PTC may occur in children and should be considered in a clinically suspicious gland. Surgery is favored over repeat FNA for most nodules with indeterminate cytology [52].

Molecular studies hold promise for complementing the results of FNA with indeterminate cytology, but they have not yet been sufficiently validated in children, and further studies are needed [53, 54]. A positive mutational test appears highly likely to be associated with malignancy, whereas insufficient data exist in children to rely on negative genetic studies to reliably exclude malignancy.

Thyroid Cancer

Thyroid nodules diagnosed in children carry a greater risk of malignancy compared to those in adults (22–26% versus 5–10% in most series) [55].Children with papillary thyroid cancer (PTC) are more likely to have regional lymph node involvement, extrathyroidal extension, and pulmonary metastasis [56]. Despite extensive disease at clinical presentation, children are much less likely to die from disease (2% or less long-term cause-specific mortality) than are adults [57].

Many children with pulmonary metastases (30–45%) develop persistent although stable disease following 131I therapy [58].

According to the Surveillance, Epidemiology, and End Results (SEER) program, new cases of thyroid cancer in people age <20 represent 1.8% of all thyroid malignancies diagnosed in the United States. Unfortunately, the incidence is increasing [59]. Among 15- to 19-year-old adolescents, thyroid cancer is the eighth most frequently diagnosed cancer and the second most common cancer among girls [57]. Adolescents have a tenfold greater incidence than younger children, and there is a female to male preponderance (5:1) during adolescence [52].

PTC accounts for 90% or more of all childhood cases. The major risk factor for developing PTC is radiation exposure to the thyroid. Children, especially those who were exposed to radiation younger than 5 years of age, are the most sensitive [60].

There are several studies suggesting that endometriosis increases risk of developing thyroid cancer compared to normal population of women without endometriosis [61, 62].

In the past, all children were treated with total thyroidectomy and ^{131}I. With increased awareness of the potential long-term side effects of ^{131}I treatment, there are increased efforts to identify patients who have a high likelihood of benefit from therapy. Current guidelines emphasize personalizing treatment and reducing unnecessary ^{131}I exposure for children who may not benefit from treatment without increasing disease-specific morbidity and mortality.

Children with DTC may experience adverse psychosocial effects and might be noncompliant with daily LT4 therapy. Attention to these possibilities and supportive counseling as needed are important in the long-term follow-up of children with DTC [63, 64].

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Chapter 25
Polycystic Ovary Syndrome in Adolescents

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Background

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting reproductive-aged women, with an estimated prevalence between 6% and 20% [1–3]. PCOS was first described by Irving Freiler Stein and Michael Leventhal as a case series of seven patients presenting with amenorrhea, irregular menses, hirsutism, infertility, and hypertrophied fibrotic ovaries with multiple follicular cysts confined to the ovarian cortex [4]. Since then, multiple diagnostic criteria for PCOS have been developed, with the Rotterdam criteria emerging as the most commonly used in adult women.

The Rotterdam criteria can be used to diagnose a patient with PCOS if they present with two of the following: ovulatory dysfunction (i.e., oligo- or anovulation), hyperandrogenism (clinical or biochemical), or poly-follicular ovarian morphology on ultrasound (greater than 12 follicles between 2 and 9 mm in diameter or ovarian volume greater than 10 cc). Other etiologies must be excluded such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, thyroid dysfunction, and hyperprolactinemia [5]. Diagnosis of PCOS in adolescents is challenging as oligomenorrhea can also present due to hypothalamic-pituitary-ovarian (HPO) axis immaturity, while acne is more common due to physiologic hormonal fluctuations. Additionally, polycystic ovaries can be difficult to identify on ultrasound since poly-follicular ovaries are more common in adolescents.

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Symptoms

The most common presenting symptom of PCOS, found in up to 90% of patients, is oligomenorrhea, though women can also present with amenorrhea, heavy menstrual bleeding, or even cyclic menses [6, 7]. Patients often present with signs of hyperandrogenism including hirsutism in 70% and acne in 15–30% of women with PCOS [3]. In addition, infertility affects 40% of women [8, 9]. Other less common presenting symptoms include weight gain or difficulty losing weight, insomnia, sleep apnea, and headaches. Since many of these symptoms, when found in isolation, may not warrant a full workup or may be related to other diagnoses, the diagnosis of PCOS is often delayed.

In a prospective cohort study, 244 predominantly Caucasian, post-menarchal girls with mean age of 15.2 years were recruited to study the prevalence of clinical and biochemical features of PCOS [10]. Irregular menstrual cycles were found in 53% of participants; however, it was not consistently associated with other clinical features of adult PCOS. Due to this physiologic irregularity, the majority of adolescents with oligomenorrhea or amenorrhea do not seek professional help [11, 12]. In this same study, hirsutism was found to be uncommon, while acne affected 70% of adolescent females. Neither feature alone was found to be directly related to PCOS, especially given that adolescents are at an age where menstrual cycles can be irregular, hair growth may be variable, and acne is common [10]. Given their frequency, clinical features such as irregular menses, poly-follicular morphology, acne, or hirsutism are not useful diagnostic features of PCOS in adolescent girls [10]. Similar rates of PCOS were also seen in patients with and without obesity (36.2% with elevated BMI vs. 32.1% in normal BMI), illustrating that obesity alone is not a helpful screening tool for PCOS [10].

Diagnosis

Expert opinion currently recommends that the diagnosis of PCOS in adolescents should consist of persistent oligomenorrhea for 2–4 years after menarche with clinical or biochemical hyperandrogenism in the absence of other etiologies [3, 13]. Ultrasound findings of polycystic ovaries are not required for the diagnosis in adolescents; however, some investigators suggest increased ovarian volume >10 cm^3 should be included in the diagnostic criteria [3].

A detailed history and physical exam, supplemented with ultrasound and blood tests, are used to support the diagnosis of PCOS. Genetic components have been linked to PCOS; therefore, taking a detailed family history can be very helpful. In addition, the physician may perform a transvaginal ultrasound, though ultrasound findings are not necessary to make the diagnosis of PCOS in adolescent females. If the adolescent is not sexually active, a transabdominal or transrectal ultrasound can be performed instead. The laboratory tests listed in Table 25.1 may be helpful to

Table 25.1 Laboratory testing in patients with oligomenorrhea and possible PCOS

Hormone	Function	PCOS
Follicle-stimulating hormone (FSH)	Stimulates follicular development	Normal or decreased
Luteinizing hormone (LH)	Stimulates ovulation	Increased
Testosterone	Sex hormone	Increased
Estradiol (E2)	Sex hormone that stimulates endometrial proliferation	Normal or increased
Sex hormone-binding globulin (SHBG)	Protein that binds to and carries estrogen, dihydrotestosterone (DHT), and testosterone in plasma	Decreased
Androstenedione	Testosterone precursor	Increased
Human chorionic gonadotropin (hCG)	Secreted by syncytiotrophoblasts in early pregnancy	No change
Anti-Mullerian hormone (AMH)	Measure of ovarian reserve	Increased

identify biochemical hyperandrogenism, which can account for the hirsutism and acne phenotype. Currently, laboratory cutoffs for the diagnosis of hyperandrogenism in adolescents have not been well studied [3]. Patients with obesity, hirsutism, or irregular menses should be identified by clinicians as high risk for PCOS, but ultimately, it may be beneficial to delay diagnosis until oligomenorrhea is persistent for 2–4 years after menarche in order to avoid overdiagnosis and unnecessary treatment [3].

Comorbidities

Women diagnosed with PCOS are at increased risk for several comorbid conditions including type 2 diabetes, obesity, hyperlipidemia, cardiovascular disease, anxiety disorder, depression, eating disorders, and sleep apnea. Fasting glucose, insulin, hemoglobin A1c (HbA1c), and lipid panels may be helpful in evaluating comorbid conditions. Psychiatric and obstructive sleep apnea screening may prompt appropriate referrals in this patient population. The relationship, if any, between PCOS and endometriosis is unknown and has not been extensively researched.

Diabetes

While the exact cause of PCOS is still unknown, insulin resistance has been suggested as a contributing factor leading to hyperandrogenism and is present in a majority of patients with PCOS. Insulin resistance means that target organs are

unable to transport glucose across cell membranes, leading to hyperglycemia and diabetes. “Therapeutic Lifestyle Changes” and nutrition are very important in patients with PCOS.

Mental Health

Numerous studies have investigated the effect of a PCOS diagnosis on quality of life in adolescents. A systematic review of published research showed increased BMI to have the strongest negative influence on quality of life in PCOS patients between 13 and 24 years old [14]. Rowlands et al. studied the psychological distress among young women (aged 18–23 years old) with PCOS or endometriosis [15]. Between 2012 and 2013, young women were recruited and surveyed using a Web-based questionnaire. Participants were contacted a year later to complete the second survey. Women who reported a PCOS or endometriosis diagnosis at Surveys 1 (history of diagnosis) and 2 (recent diagnosis) had greater odds of reporting moderate to severe psychological distress when compared to women who had never been diagnosed with either condition. Additionally, young women who were recently diagnosed with PCOS or endometriosis (Survey 2) were found at greater risk of moderate to severe distress in the year leading up to diagnosis compared to women without either condition.

Endometriosis

There are multiple biochemical mechanisms underlying both endometriosis and PCOS that are now being elucidated. Both diseases have been described in the literature to be associated with aberrant estrogen receptor expression, aromatase activity, and increased reactive oxygen species [16–18].

Hart and Doherty examined the potential implications of a PCOS diagnosis on a woman’s long-term health in 2015 and found women with PCOS had more hospitalizations for gynecologic conditions. This population was also shown to have a greater chance of receiving an endometriosis diagnosis (26.4 vs. 4.4%, $p < 0.001$) when compared to women with PCOS without hospitalization. Additionally, women with PCOS experience higher rates of menstrual problems including earlier reported menarche, menorrhagia, and irregular or infrequent menses [19]. Additional research is necessary to determine any stronger links between PCOS and endometriosis.

Treatment Options

Diet and Exercise

Lifestyle changes are the first-line treatment for PCOS. If a patient is obese, losing weight may help with ovulation induction, regulating menstrual cycles, improving hyperinsulinemia, and reducing the chance of developing comorbid conditions such as cardiovascular disease and type II diabetes [14, 20]. Five percent weight reduction can lead to regular menstrual cycles in women with amenorrhea.

Medical Management

Treatment should be aimed at managing the adolescent's most bothersome symptoms, including but not limited to irregular menses, hirsutism, acne, and infertility. The most common recommended medical treatment for irregular menses is combined hormonal contraceptives for adolescents who are not currently attempting conception. Treatment options are summarized in Table 25.2. Letrozole is currently

Table 25.2 Medical management options for symptoms associated with PCOS

Ovulatory dysfunction/irregular menses	
Combined oral contraceptive	Management of irregular menses, hirsutism, and acne; can decrease risk of endometrial hyperplasia and malignancy with long-term use (>10 years)
Progestin-only pill	Cyclic progestin used to induce withdrawal bleeding; can decrease risk of endometrial hyperplasia and malignancy
Metformin	Decreases insulin resistance; promotes weight loss and ovulation induction
Clomiphene citrate, letrozole	Ovulation induction
Clinical hyperandrogenism (acne, hirsutism)	
Combined oral contraceptive	
Spironolactone	Decreases androgen levels for treatment of hirsutism and acne
Chemical depilatories (creams, gels, and lotions)	Destroys hair follicles
Electrolysis or laser therapy	Destroys hair follicles
Overweight/obesity	
Metformin	
Orlistat	Decreases absorption of dietary fats; lowers cholesterol levels
Lorcaserin	Induces anorexia

the first-line medical therapy for ovulation induction in patients with PCOS attempting conception, but clomiphene citrate and metformin are other reasonable alternatives [21]. Of note, medical therapies for hirsutism are not generally FDA approved for that indication [3].

Surgical Management

Laparoscopic ovarian drilling (LOD) or laparoscopic ovarian diathermy has historically been performed in PCOS patient's refractory to medical management. Through a minimally invasive technique, an instrument is inserted through the abdomen to "drill" holes in the ovary causing changes in hormone levels and triggering ovulation. Ovarian drilling performed in patients with clomiphene-resistant PCOS resulted in 66% of patients having spontaneous menses after surgery and 50% becoming pregnant after therapy [22]. LOD is associated with restoration of ovulation in 80–90% of cases; furthermore, subsequent medical induction of ovulation may be more successful [23].

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Chapter 26
Benign Adnexal Masses in Pediatric and Adolescent Females

Erica C. Dun and Serena Wong

Introduction

Adnexal masses are rare in the pediatric and adolescent population, occurring in 2.6 per 100,000 girls [1]. Fortunately, most adnexal lesions are benign functional cysts and neoplasms, with only 9–11% of adnexal masses in this age group ultimately diagnosed as malignant [2]. Though malignancy is less common, the goal of the diagnostic evaluation is to determine the origin of the mass (ovarian, tubal, uterine, or nongynecologic) and exclude malignancy. This chapter will explore the workup and common gynecological and nongynecological etiologies of adnexal masses in children and adolescents.

Diagnosis

Among young females diagnosed with a pelvic mass, the most common presenting symptoms are acute and chronic abdominal pain, bloating, distension, nausea, and vomiting, and less common are precocious puberty, hirsutism, and abnormal vaginal bleeding. While these symptoms are shared by many pediatric and adolescent pathologies, medical and family history, physical exam, laboratory testing, and imaging can assist in the differential diagnosis.

Eliciting symptoms from adolescents may be challenging and complaints nonspecific. Simplified questions and thorough review of systems may assist in paring

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Table 26.1 Differential diagnosis of adnexal masses in pediatric and adolescent females

Ovarian	Functional cyst, paraovarian cyst, endometrioma, mature cystic teratoma (dermoid cyst), serous or mucinous cystadenoma, borderline tumors, malignant tumors
Tubal	Paratubal cyst, hydrosalpinx, tubo-ovarian abscess, ectopic pregnancy
Uterine	Müllerian anomalies, leiomyomas, hematometra
Urinary	Urachal cyst, pelvic kidney, hydronephrosis, Wilms tumor, ureteral diverticulum, bladder diverticulum
Gastrointestinal	Appendiceal abscess or mucocele, mesenteric cyst, diverticular abscess, gastrointestinal cancers, retroperitoneal sarcomas
Other	Metastatic cancers from the breast, stomach, and colon

down the broad differential of abdominal and pelvic masses (Table 26.1). If possible, obtaining a history of the problem with relation to the duration (acute, chronic, or cyclical), the quality of the pain (sharp or visceral), and gynecologic history including menarche or lack of menstruation, menstrual patterns and irregularities, sexual activity, and risk for pregnancy and sexually transmitted infections, can be helpful in narrowing the differential.

Assessing family history for hereditary cancer syndrome risk should be included in the initial history taking. Hereditary breast and ovarian cancer syndrome (HBOC) related to the breast cancer (*BRCA*) inherited mutations in the *BRCA1* and *BRCA2* genes increases the lifetime risk for epithelial ovarian cancer: 35–46% for *BRCA1* carriers and 13–23% for *BRCA2* carriers [3]. For women with *BRCA1* and *BRCA2* mutations, there is an earlier onset of ovarian cancer with a median age at diagnosis of 42 years (range, 28–55 years) [4]. *BRCA1* and *BRCA2* gene-related cancers have not yet been reported in pediatric and adolescent populations. For females diagnosed with *BRCA1* and *BRCA2* mutations, the National Comprehensive Cancer Network (NCCN) recommends initial screening in early adulthood at ages 20–25 years, or 5–10 years earlier than the youngest age at cancer diagnosis in the family [5]. Lynch syndrome also known as hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) both predispose people to early-onset colorectal cancer [6]. Women with Lynch syndrome have a 5–10% increased lifetime risk of ovarian cancer through age 70 [7]. FAP in particular predisposes those affected to adenomatous polyps during adolescence with progression to colorectal cancer (CRC) by middle age; the incidence of CRC approaches 100% by the age of 50 years [8]. As a result, for those with FAP, screening with flexible sigmoidoscopy or colonoscopy for CRC begins at 10–15 years old and is repeated at a yearly interval. People affected by HNPCC begin screening at a later age 20–25 years old or 2–5 years before the earliest CRC diagnosis and at 1- to 2-year intervals [9].

Physical examination of virginal pediatric and adolescents may be limited, but external characteristics, abdominal palpation, and rectal examination can be performed. Primary amenorrhea and pelvic mass in an older adolescent female may suggest a Müllerian anomaly. Discordant Tanner stage and presence of early menarche and thelarche could suggest an estrogen-producing granulosa cell tumor or thecoma. Androgen-secreting tumors such as Sertoli–Leydig cell, lipid cell, or hilus cell tumors may virilize young females, causing excessive hair growth, severe acne, increased muscle mass, and clitoromegaly.

When abdominal and pelvic masses are suspected, ultrasound is the recommended initial imaging modality for both adolescents and adults. The primary goal of ultrasound is to distinguish benign, simple cystic structures from solid and complex masses that are concerning for malignancy, in addition to assisting in determining the origin of the adnexal mass either within the gynecologic, urologic, or gastrointestinal tracts. Ultrasound algorithms developed for ovarian cancer risk stratification in adult females cannot be translated to the pediatric and adolescent population because of the diversity of pediatric and adolescent ovarian tumors, whereas most adult ovarian tumors are epithelial in origin. However, in pediatric and adolescent populations, most malignant masses are significantly larger than benign masses, on average 17.3 ± 7.1 cm versus 8.8 ± 7.1 cm, respectively ($p < 0.001$) [10]. If ultrasound imaging is indeterminate or there is a concern for malignancy, then CT scan and/or MRI can be used to aid diagnosis. The benefit of MRI is no ionizing radiation, which is advantageous in the pediatric and adolescent population. MRI can better differentiate soft tissues of the pelvis to assist in the diagnosis of suspected Müllerian anomalies or distinguish between nonovarian masses such as pedunculated uterine fibroids [11, 12].

In the workup of a pelvic mass, initial laboratory testing includes a complete blood count to assess for infection and pregnancy test in reproductive age females to rule out urgent pregnancy-related adnexal masses, that is, ectopic pregnancy. Depending on the medical history, physical exam, and diagnostic imaging, if a possibility of malignancy is suspected, serum tumor markers could be performed. Although epithelial ovarian cancers are the most common histology in adults, among the pediatric and adolescent population it only represents 1.9% of ovarian neoplasms [13], thus cancer antigen (CA 125) levels are seldom elevated. CA 125 levels are mildly elevated in a handful of benign conditions such as endometriosis, pregnancy, pelvic inflammatory disease, and nongynecologic cancer. Carcinoembryonic antigen (CEA) is elevated in cases of colorectal cancer, and CA 19-9 elevation is present in pancreatic cancer, specifically cancer of the exocrine pancreas. However, malignant ovarian tumors among adolescents are diverse, and they include germ cell tumors (immature teratomas, embryonal carcinomas, yolk sac tumors, and choriocarcinoma), sex cord stromal tumors (sertoli, granulosa, and theca cell), tumors of low-malignant potential, and metastatic cancers of the breast, colon, stomach, and appendix. Elevations of certain tumor markers and hormones can help differentially diagnose germ cell tumors (Table 26.2) and sex cord stromal tumors (Table 26.3).

Table 26.2 Serum biomarkers in ovarian germ cell tumors

	β-hcg	AFP	LDH	CA 125
Dysgerminoma	+	−	+	−
Endodermal sinus tumor (also Yolk sac tumor)	−	+	−	−
Choriocarcinoma	+	−	−	−
Immature teratoma	−	+	+	+
Embryonal carcinoma	+	+	−	−

Table 26.3 Serum biomarkers in ovarian sex cord stromal tumors

	Estrogen	Progesterone	Inhibin B	Androgens
Sertoli cell tumor	+	+	–	–
Granulosa cell tumor	+	–	+	–
Theca cell tumor (also Thecoma)	+	–	–	±
Sertoli–Leydig cell tumor	–	–	–	+

Management

The majority of pediatric and adolescents ovarian tumors are benign. Thus, there are possible nonsurgical options depending on the diagnosis. Reimaging benign-appearing ovarian cyst after 2–3 menstrual cycles in postmenarchal girls is apt show resolution of the cyst. In adolescents with benign-appearing and persistent cysts and masses, the movement is toward fertility-sparing surgery with retention of as much of the affected ovary as possible to avoid decreased future fertility and premature castration. In fact, adolescents receiving a unilateral salpingo-oophorectomy have a 3–15% lifetime risk of torsion or neoplasia in the contralateral ovary and are more often referred for infertility evaluation [14, 15].

Among pediatric and adolescent patients with larger and persistent adnexal ovarian masses, the primary goal is risk stratification for malignancy. Treatment of the mass should balance appropriate surgical management with preservation of future reproductive capability. Concern regarding inadequate resection or staging in the setting of a malignancy may place the patient at risk for unnecessary adjuvant therapy or recurrent disease, yet at the same time, aggressive treatment of a patient with a nonmalignant mass may lead to future infertility. Preoperative malignancy risk assessment is essential to achieve a balance.

In a recent systematic review by the American Pediatric Surgical Association, factors that were the most helpful in predicting the preoperative cancer risk were tumor markers and diagnostic imaging [16]. Tumor markers when ordered as a standard panel preoperative have excellent positive predictive value, accuracy, and association with malignancy with both germ cell and epithelial tumors in a prospective study [17] and two retrospective studies [18, 19].

Ultrasound studies found that tumor size and volume were good preoperative predictors in this population, with a larger diameter and increased volume associated with an increased likelihood of malignancy. In a study by Oltmann et al., a tumor size ≥8 cm had an odds ratio of 19 for malignancy (95% CI, 4.42–81.69) [18]. In a study by Papic et al., an ovarian mass diameter ≥10 cm had an odds ratio of 9.6 for malignancy (95% CI, 2.12–43.42) [19]. A study by Abbas et al., demonstrated that a tumor volume ≥194 mL using the "prolate ellipsoid formula" that measure nonuniform spheroid structures had a 100% sensitivity, 54% specificity, negative predictive value (NPV) of 100%, and positive predictive value (PPV) of 13% for malignancy [20]. Evaluation of the tumor composition found that the presence of sold components increased the odds of malignancy up to six-fold [19–21]. Cystic appearance had a high sensitivity (100%) for benign disease [21].

An ultrasound scoring system called the Ueland index combines size and intrinsic mass characteristics that increase the sensitivity, specificity, and accuracy of ultrasound as a preoperative screening modality for malignancy. Among the first scoring systems developed by DePriest et al. in a retrospective population of pediatric and adult patients was an ultrasound morphology index that included volume, wall structure, and septations [22]. Ueland modified the DePriest scoring system into a two-factor system and focused on patients less than 20 years with both epithelial and germ cell tumors. The Ueland index ≥7 had a 90% sensitivity, 94% specificity, and positive likelihood ratio of 35.870 for predicting malignancy [23]. The ovarian crescent sign (OCS) is another radiological indicator of nonmalignancy. This finding is present or "positive" and indicates a benign tumor when a rim of healthy ovarian tissue is seen on the same ovary that has the ovarian mass. In the pediatric literature, the OCS compared favorably with the Ueland index; OCS absence was 90% sensitive and 72% specific for predicting malignancy [24].

When there is a high suspicious of malignancy prior to surgery, the Children's Oncology Group (COG) has several recommendations: (1) ascites for cytology or peritoneal washings if no ascites present; (2) inspect the omentum, resect only if abnormal; (3) inspect and palpate iliac and para-aortocaval nodes, perform biopsy only if abnormal; (4) inspect and palpate contralateral ovary, perform biopsy only if abnormal; (5) intact removal of the tumor, for resectable tumors; and (6) primary resection for localized tumors, perform biopsy only if resection would require sacrifice of other organs and plan for postchemotherapy resection [25].

Gynecologic Adnexal Masses

Ovarian Masses

Functional Ovarian Cysts

Ovarian cysts are rarely detected in female children age 5–9; those cysts detected on ultrasound are typically <3 cm in diameter and simple. With the onset of adolescence, the ovary is more active due to increased gonadotropin secretion. Ovarian cyst frequency rises and reaches 3.8–30.9% in early adolescence, 26.7–31.3% in middle adolescence, and 13.6% in late adolescence. Peak ovarian cyst frequency was 15 years with a rate of 31.3% in a population of females aged 5–18 years who had ultrasounds in a pediatric emergency room for pelvic pain [26]. Functional ovarian cysts have typically clear fluid contents, and because the clear fluid permits passage of ultrasound waves without echoes, the resulting image is a simple, echolucent appearance, represented as black areas on ultrasound imaging (Fig. 26.1).

Corpus luteum cysts (Fig. 26.2) are another benign physiologic cyst of the ovary that occur after the ovum has been released from the ovarian follicle. The ruptured follicle produces estrogen and progesterone for implantation of the embryo, and if pregnancy does not occur, then the corpus luteum typically breaks down and

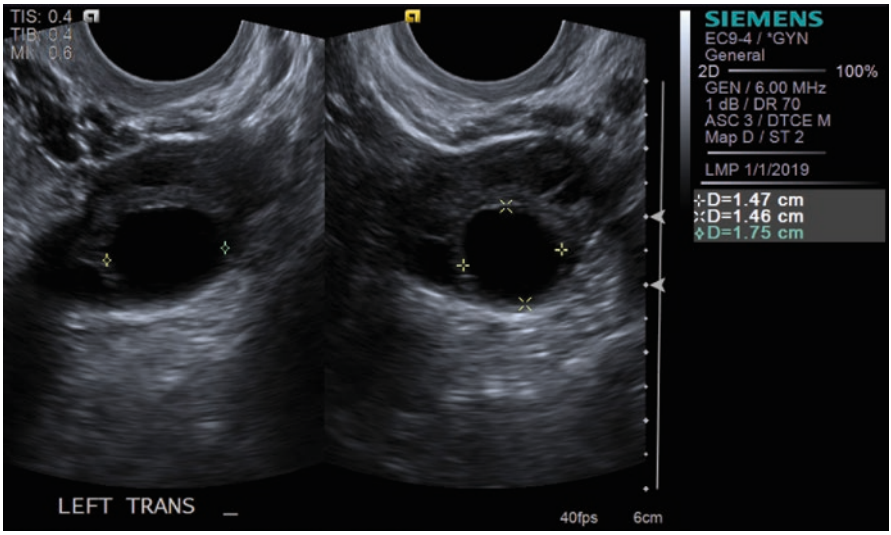


Fig. 26.1 Appearance of a functional cyst of the left ovary as viewed on transvaginal ultrasound, typically functional cysts are <3 cm in diameter, simple, without septations or solid components

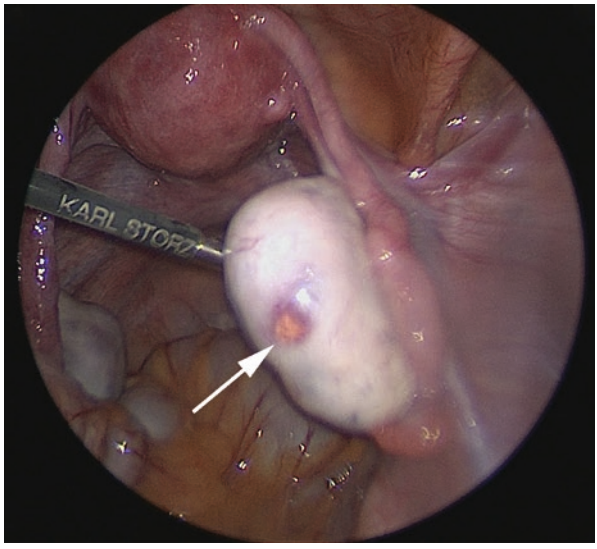


Fig. 26.2 Laparoscopic image of corpus luteum cyst (arrow) of the right ovary

disappears. Sometimes the corpus luteum fails to regress and enlarges with or without hemorrhage. Cysts with hemorrhage are often described as hemorrhagic ovarian cysts or hemorrhagic corpus luteum cysts, and can cause severe pain when they rupture and blood irritates the parietal peritoneum. Ultrasound findings of the corpus luteum include a diffusely thick wall, "ring of fire" peripheral vascularity, <3 cm in diameter, and crenulated inner margin and internal echoes. Benign functional

cysts typically resolve within 3 months, thus imaging to differentiate benign and pathologic ovarian cysts is recommend with an interval of 3 months [27]. Early studies of combined oral contraceptives containing (COCs) ethinyl estradiol and progesterone were associated with reduced incidence of functional ovarian cysts. As a result, the clinical practice of prescribing COCs to treat recurrent, painful ovarian cysts has been ongoing since the 1970s. However, a recent Cochran meta-analysis found that most cysts resolved without treatment within a few cycles and treatment with COCs did not hasten resolution of functional ovarian cysts [28]. Observation for 2–3 cycles is also an appropriate management option.

Mature Cystic Teratomas of the Ovary

Dermoid cysts of the ovary also called mature cystic teratomas (derived from the Greek word *teras* meaning "monster") are common benign ovarian mass. They occur bilaterally in 10–15% of cases [29]. The origin of the term refers to the shared embryologic origin of the tumor cells from germ cells. Primordial germ cells in the developing embryo migrate from the yolk sac along the midline and paraxial regions of the embryo to the genital ridge. At the genital ridge, ovaries develop in the absence of the SRY gene [30]. The migration of germ cells along the midline explains why germ cell tumors in children occur most commonly in the midline or in the gonads. The totipotent germ cells differentiate abnormally into mature ectodermal structures such as hair, teeth, and sebum (Fig. 26.3) within the ovary and rarely the vagina [31]. In only 1–2% of all teratomas, there are immature elements that contain all three embryonic germ cell layers and lack full differentiation [32]. Teratomas with immature elements are called immature teratomas and considered germ cell malignancies [33].

Mature cystic teratomas typically contain fluid, fat, and solid tissue and may have a variety of appearances on ultrasound (Fig. 26.4). However, the three most common findings are (1) a cystic lesion with a densely echogenic tubercle projecting into the cyst lumen, (2) a diffusely or partially echogenic mass with an echogenic area owing to sebaceous material and hair, and (3) multiple thin, echogenic bands cause by hair in the cyst cavity. Pure sebum can appear hypoechoic or anechoic. Fluid–fluid levels result from sebum floating above aqueous fluid, which appears more echogenic than the sebum layer. The dermoid plug appears echogenic with shadowing due to adipose tissue or calcifications within the plug or hair arising from it [34]. Teratomas larger than 5–6 cm are at risk of ovarian torsion, and nonurgent laparoscopic removal is recommended to prevent a future gynecologic emergency. Torsion may occur in 15% of cases, increasing with increasing size [35]. These cysts are generally easy to separate from normal ovarian tissue (Fig. 26.5), and the goal is to prevent intra-abdominal spillage of the contents to prevent postop peritonitis. If spillage occurs, copious intraoperative irrigation is performed to remove most or all of the spilled contents. Recurrence of benign, mature teratomas is 11%, for which 3% may need another surgical procedure [36]. Histologically, mature teratomas contain sebaceous glands and epidermis (Fig. 26.6) with keratinous debris.

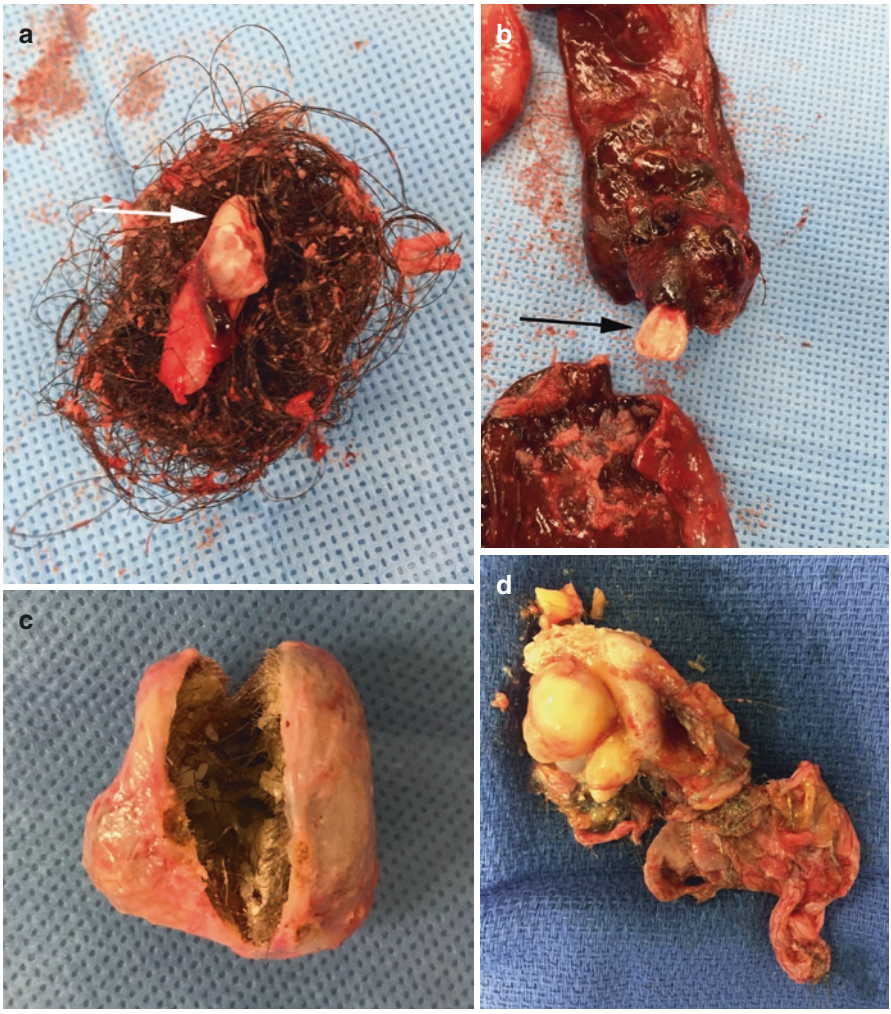


Fig. 26.3 (**a**) Gross image of a mature cystic teratoma with a molar tooth (arrow) surrounded by hair and sebum. (**b**) Gross image of a mature cystic teratoma with an incisor tooth (arrow) attached to tissue. (**c**) Gross image of a mature cystic teratoma with hair and sebum. (**d**) Gross image of a dermoid plug with adipose tissue, hair, and sebum

Ovarian Serous and Mucinous Cystadenomas

Ovarian cystadenomas are common benign epithelial neoplasms, accounting for up to 40% of noncancerous ovarian tumors [37]. They occur in females of all ages, though less commonly in children and adolescents. The most frequent types are serous and mucinous cystadenomas. Rarer histologies of cystadenomas include the endometrioid cystadenoma, clear cell cystadenoma, and seromucinous cystadenoma.

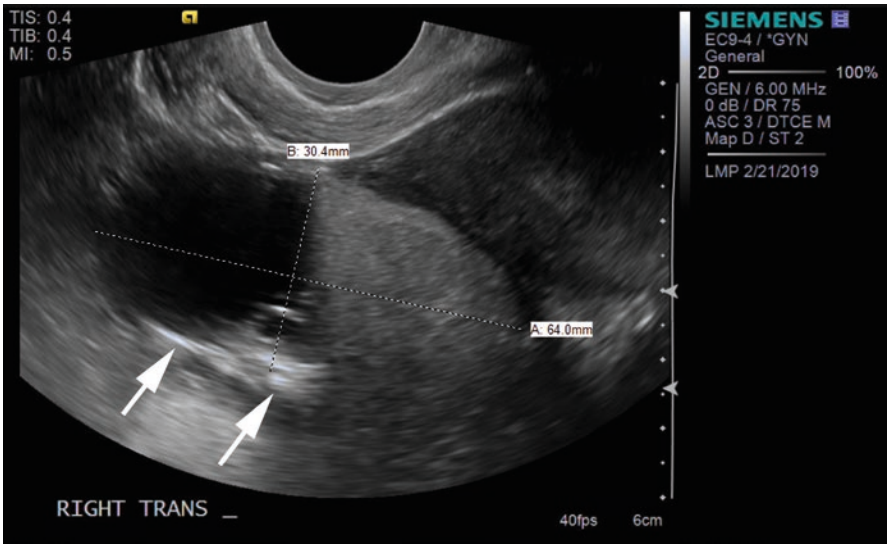


Fig. 26.4 Transvaginal ultrasound of right ovary showing a complex mass containing echogenic areas (arrows) and cystic components consistent with a 6-cm mature cystic teratoma or dermoid cyst of the ovary

Serous cystadenomas develop as hyperplastic expansion from epithelial inclusions. Most are polyclonal, but monoclonal cystadenomas exist. These cysts can range in size from 1 to more than 30 cm in diameter with a mean size of 5–8 cm. They can grow rapidly, filling the abdomen and pelvis (Fig. 26.7) before symptoms occur. In 15% of cases they are present in both ovaries [38]. They have a smooth outer surface and contain one or more thin-walled cysts containing clear, straw colored, watery fluid.

Mucinous cystadenomas may be of germ cell origin, but the tumorigenesis of these masses is not fully understood. Genetic studies have identified V-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS) mutations in up to 60% of the tumors [39]. Mucinous cystadenomas also have smooth surfaces and are typically multilocular. They range in size from a few to greater than 30 cm with a mean size of 10 cm. Most (>95%) are unilateral.

Ultrasound is again the best modality for detecting and diagnosing these neoplasms. Serous cystadenomas appear as smooth, thin-walled, anechoic, fluid-filled structures. Mucinous cystadenomas are also thin walled, large, and unilateral. They have internal thin-walled locules containing mucin that appears as fluid with low-level echogenicity. Neither type of cystadenomas is associated with significant vascularity [40]. CA-125 can be used to help distinguish benign cystadenomas from potential epithelial ovarian carcinomas. When these tumors become giant-sized such as this serous cystadenoma (Fig. 26.7), then ultrasound has limited range and another modality, either CT or MRI, can be employed to image the whole extent of the ovarian pathology. Larger or symptomatic cystadenomas should be treated with

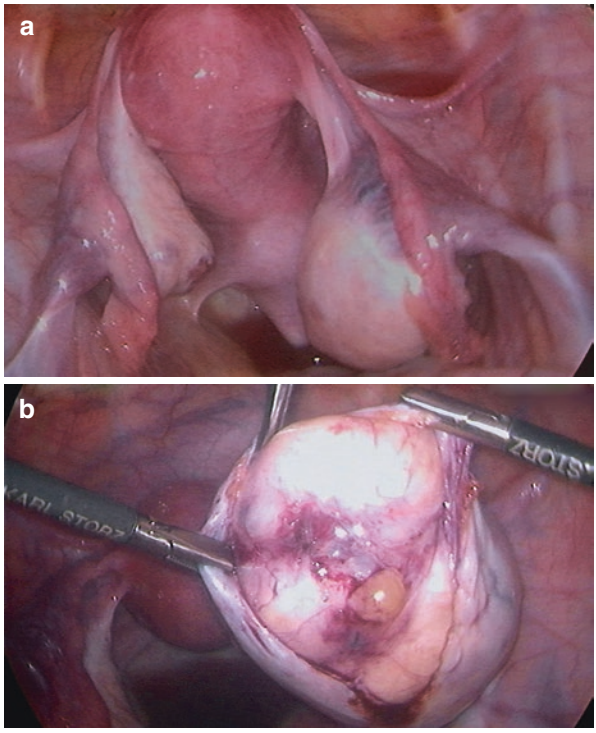


Fig. 26.5 (**a**) Laparoscopic view of right ovarian mature cystic teratoma prior to removal. Note that the right ovary with the teratoma is significantly larger. A small functional cyst is present in the left ovary. (**b**) Laparoscopic cystectomy of the right ovarian mature cystic teratoma. The ovary was incised in a linear fashion and the teratoma enucleated

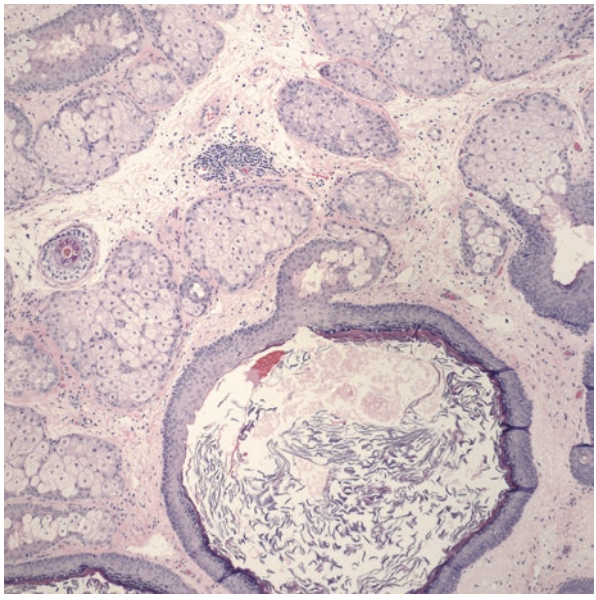


Fig. 26.6 Mature cystic teratoma magnified at 10×. Histologically, the mature cystic teratoma has numerous sebaceous glands and epidermis with associated keratinous debris

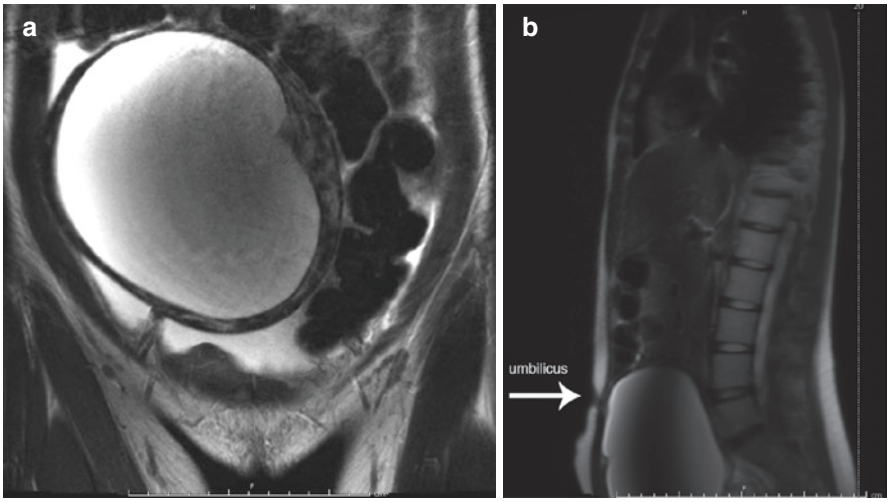


Fig. 26.7 MRI abdomen, T2-weighted. (**a**) Coronal view of a 22-cm simple serous cystadenoma. (**b**) Sagittal view, the superior aspect of the serous cystadenoma is above the patient's umbilicus (arrow)

cystectomy and ovarian preservation in pediatric and adolescent populations. Recurrence rate in the pediatric as well as adult literature for both serous and mucinous cystadenomas is low, and there are no reported deaths related to benign mucinous cystadenomas [41–43].

Adnexal Torsion

Adnexal torsion is the partial or complete twisting of the vascular pedicle in the suspensory ligament or infundibulopelvic ligament resulting in obstruction of lymphatic, venous, and arterial flow. Adnexal torsion is a term that is inclusive of the ovary, fallopian tube, or both. Concomitant ovarian and tubal torsion has been shown to occur in up to 67% of cases of adnexal torsion [44, 45]. Isolated fallopian tube torsion is very rare occurring only 1 in 1.5 million females [46]. Torsion can occur in females of all ages, but most commonly during adolescence with increased ovarian activity and during pregnancy. Only 15% of torsions occur in pediatric populations. The peak incidence occurs during early adolescence and immediate postmenarchal years; 50% of cases occur in girls between 9 and 14 years of age [47] and 17–20% of cases occurring in pregnancy [48]. The most frequently encountered adnexal lesions are mature cystic teratomas and follicular cysts. Malignancy is involved in 1.8–5.4% of pediatric and adolescent torsion cases, with greater likelihood of malignancy if the mass is >8 cm [49–51]. Risk of recurrent torsion in pediatric patients is between 5% and 18% [52, 53].

Acute lower abdominal pain, nausea, vomiting, mild fever, and leukocytosis may be signs of acute torsion. “Waves” of acute pelvic pain with nausea may suggest intermittent torsion. These symptoms are altogether nonspecific, and as a result, imaging in particular ultrasonography may be heavily relied on to diagnose adnexal torsion. The most constant finding in ovarian torsion is a unilaterally enlarged ovary (>4 cm) compared with the contralateral ovary, which may appear solid with early torsion or heterogeneous with late torsion. The heterogeneous appearance is due to edema, admixed with necrosis. A specific ultrasound sign described in association with ovarian torsion in adolescents is the presence of multiple follicles at the periphery of a unilaterally enlarged edematous ovary. Free pelvic fluid in the cul-de-sac has been detected in up to 87% of cases of ovarian torsion [44, 54, 55]. Color Doppler ultrasound evaluation is often used to assist with the diagnosis of torsion. However, the Doppler flow is highly variable based on the degree of vascular compromise. The ovaries have a dual arterial supply from the ovarian artery and the adnexal branch of the uterine artery. The classic color Doppler sonographic finding in ovarian torsion is the absence of arterial flow. But in a study of surgically confirmed ovarian torsion, the absence of arterial flow was found in only 73% of cases [44]. In another study, 60% of patients with torsion had normal color Doppler flow findings [56]. Thus, no arterial flow is specific for torsion but may not exclude torsion. Arterial flow is typically reduced with a concomitant venous flow abnormality. Decreased or absence of venous flow (93%) is more commonly found and reflects early collapse of the compliant vein walls. Arterial walls are thicker and resist collapse, and thus arterial occlusion is a later finding in torsion cases.

Adnexal torsion is a surgical emergency, and in adolescent females, fertility-sparing surgery is prioritized because of the low risk of malignancy. Clinical appearance of the ovary at the time of surgical detorsion may not be the best indicator of parenchymal viability; therefore, ovarian tissue preservation despite the appearance has been advocated. Severely compromised ovaries and fallopian tubes with purple-black, mottled appearance (Fig. 26.8) have been found to be functional on postoperative imaging. At most pediatric hospitals, there has been a paradigm shift from oophorectomy to ovarian preservation for uncomplicated torsion. In a study of 43 girls (mean age 8.3 years) who underwent operations for torsion and had ovary-sparing surgery, ovarian preservation was accomplished in 37 (86%) patients, while 6 (13%) underwent oophorectomy. Of the patients who had ovarian preservation, postoperative ovarian imaging showed that 25 of 34 (74%) patients had viable follicles visualized in the previously torsed ovary. Recurrent torsion was 7% in the study [57]. In general, recurrent torsion is likely because of anatomic predisposition, including laxity within the utero-ovarian ligaments, long fallopian tubes, and lack of adnexal mass. Oophoropexy has been proposed as a means of decreasing recurrence. While there is no clear evidence to support oophoropexy in patients who present with a first episode of ovarian torsion, some experts advocate it for patients with recurrent ovarian torsion. Other experts discourage use of oophoropexy altogether, suggesting that it may have a negative impact on fallopian tube development and fertility due to potential alterations in anatomy and blood supply [58]. Ultrasound at 3 months after detorsion surgery should be performed to document ovarian

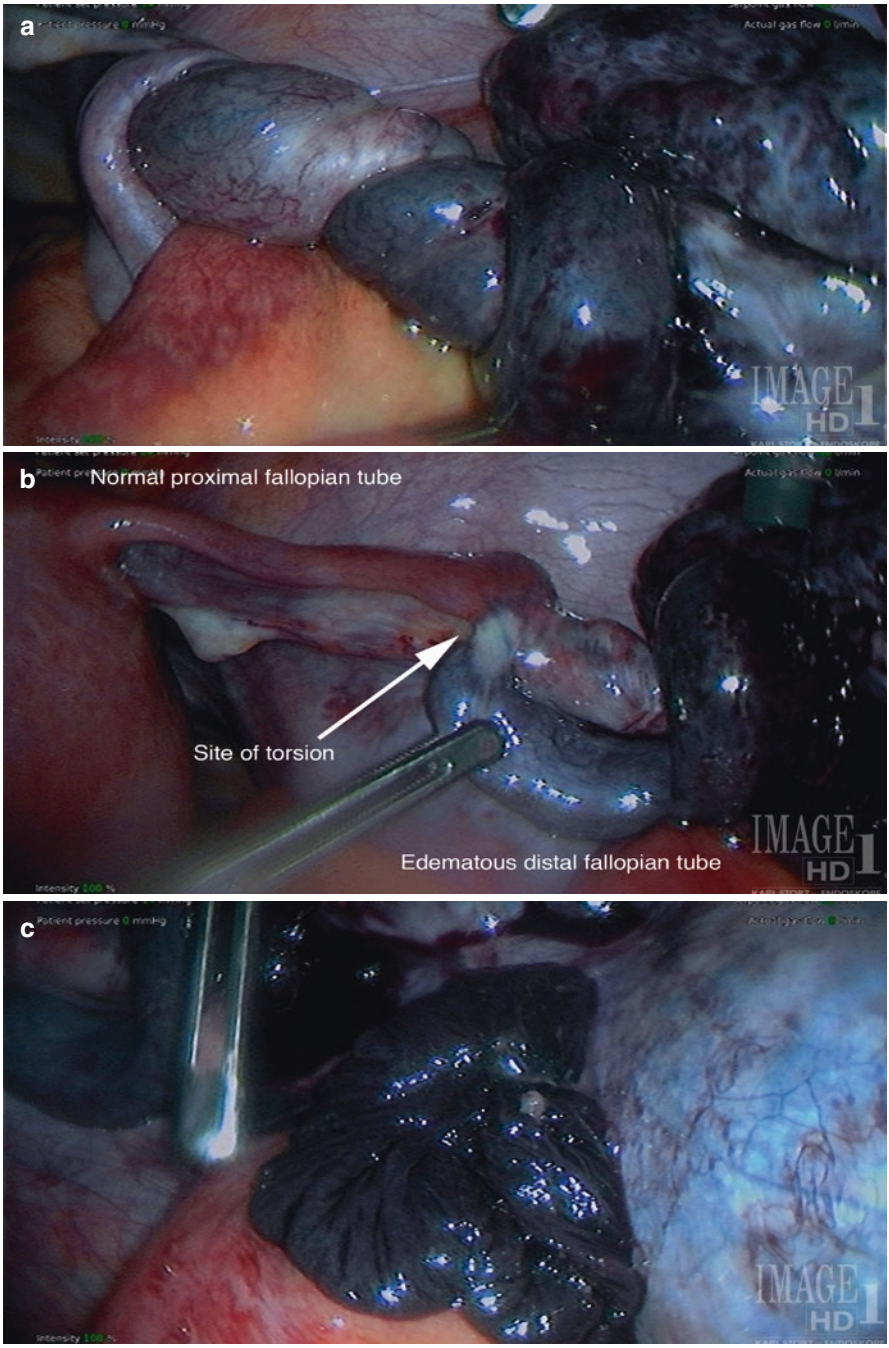


Fig. 26.8 (**a**) Torsed 5× left ovary and fallopian tube causing severe edema and dark discoloration beyond dusky. (**b**) After the pedicle is untwisted, the torsed organ should be allowed to reperfuse and reexamined later on during the procedure for signs of viable tissue. (**c**) The dark fimbriae of the torsed fallopian tube

viability or the presence of ovarian follicles and determine if there is a concurrent malignancy if there was a perioperative concern for neoplasm and pathology is nondiagnostic.

Endometriomas and Endometriosis

Endometriosis or ectopic endometrium implanted outside the uterus affects 10–15% of reproductive-aged women [59] and up to 70% women with chronic pelvic pain [60]. Among adolescents undergoing laparoscopy for chronic pelvic pain and dysmenorrhea, rates of laparoscopically confirmed endometriosis are less established, but estimates range from 19% to 73% [61]. In a small cohort of adolescents diagnosed with endometriosis, the mean age at diagnosis was 17 years, and the mean from the onset of symptoms until diagnosis was 23 months, after being evaluated by an average of three physicians [62]. Endometriosis is the leading cause of secondary dysmenorrhea in adolescents, and it should be considered with persistent, clinically significant dysmenorrhea despite treatment with hormonal medication and nonsteroidal anti-inflammatory drugs.

Diagnosis of endometriosis is primarily surgical. However, the presence of an endometrioma on preoperative imaging is highly suggestive that deeply infiltrating endometriosis (DIE) is present [63, 64]. Ultrasound is main imaging modality used to diagnose endometriomas like other pelvic masses. The classic appearance of an endometrioma (Fig. 26.9a) on ultrasound is a unilocular cyst with low-level homogenous "ground glass" echogenicity representing old blood within the cyst. The cyst wall is regular and thick, and it has minimal flow [65]. If further imaging to assess the extent of the DIE, MRI with T1 and T2 weighting can help establish a diagnosis of endometrioma with specificity greater than 90% [66]. Endometriomas have high signal intensity on T1-weighted MR images and signal

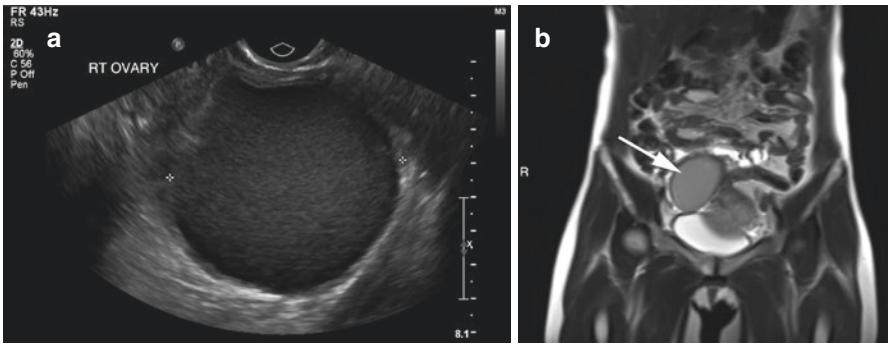
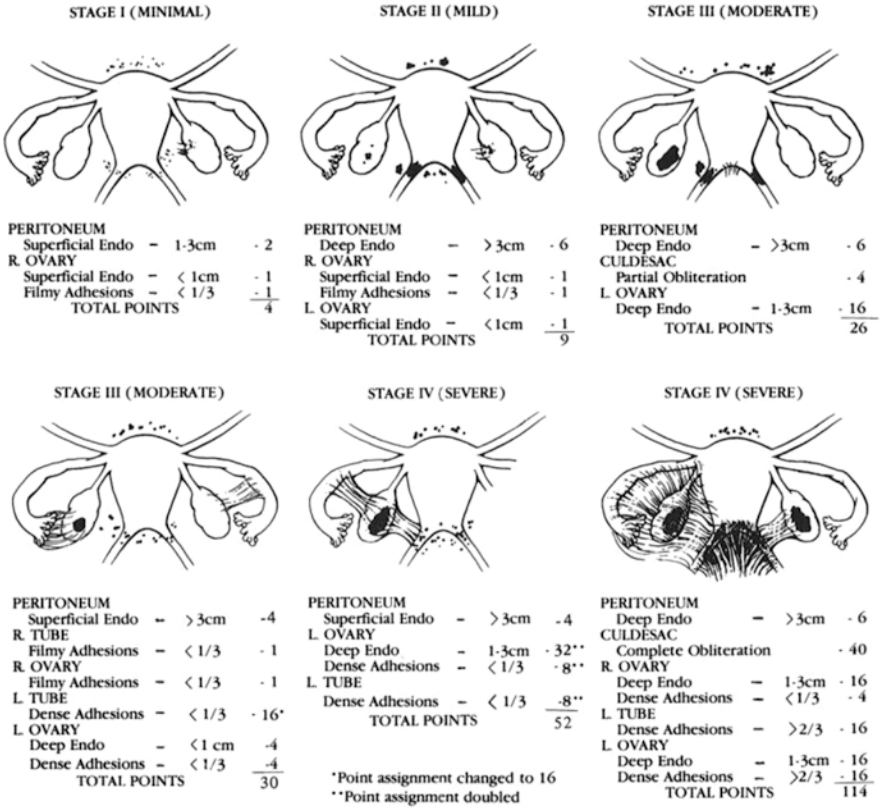


Fig. 26.9 (**a**) Ultrasound of an endometrioma of the right ovary has characteristic unilocular tumor with low-level echogenicity "ground glass" appearance representing old blood. (**b**) Coronal T2-weighted MRI of the same endometrioma (arrow) shows a unilocular, hypointense mass

intensity lower than simple fluid on T2-weighted MR images appearing hypointense (Fig. 26.9b) due to the presence of deoxyhemoglobin and methemoglobin. DIE involving the uterosacral ligaments, anterior rectosigmoid colon, bladder, uterus, and cul-de-sac has poorly defined margins and T2 signal hypointensity as a result of fibrosis [67].

Laparoscopic findings of endometriosis in adolescents may appear different than in adults. Adolescents with endometriosis tend to have superficial lesions and are more often diagnosed with early (Table 26.4) stage I or II disease [62]. Adolescent endometriosis lesions may have a vesicular appearance (Fig. 26.10) and are clear or red (Fig. 26.11) in color. Nevertheless, the superficial peritoneal disease is thought to be highly inflammatory, and the clear and red lesions may be the most painful [68]. Endometriomas appear enlarged with normal appearing ovarian cortex (Fig. 26.12a), but upon rupture of the contents spill the characteristic "chocolate cyst" (Fig. 26.12b) consisting of old blood.

Table 26.4 American Society for Reproductive Medicine (ASRM) Revised Classification of Endometriosis 1996 [101]



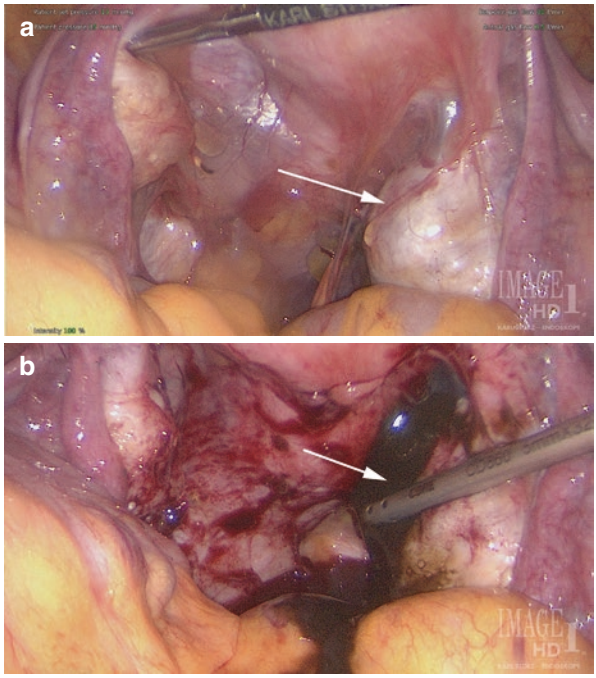


Fig. 26.10 (**a**) Laparoscopic view of stage 3 endometriosis with bilateral adnexal adhesions, inclusion cysts, and right ovarian endometrioma prior to excision. (**b**) Rupture of the right ovarian endometrioma resulted in oozing of the thick, brown, "chocolate cyst" contents

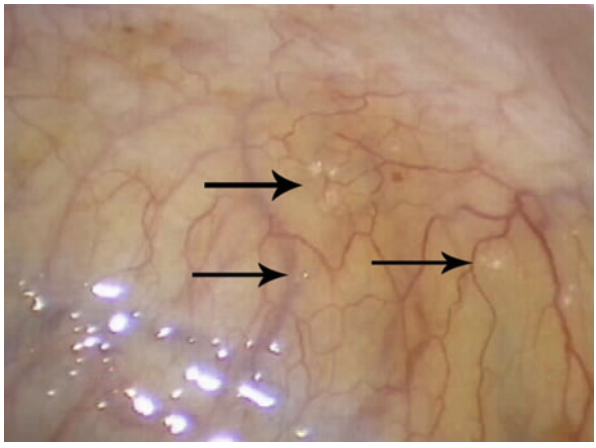


Fig. 26.11 Atypical clear endometriosis lesions studding the peritoneum of the posterior cul-de-sac. The clear, vesicular, superficial lesions (arrow) were found in an 18-year-old patient with stage I endometriosis who had a family history of the disease

Although there is an ongoing debate over techniques for treating endometriosis, evidence supports cystectomy (removal of the entire cyst wall) over incision and drainage of the endometrioma for improved pain, decreased recurrence, and higher fertility rates [69]. Postoperative hormonal suppression options for adolescents include combined oral contraceptive pills, progesterone-only pills, medroxyprogesterone acetate, levonorgestrel intrauterine device, and leuprolide depot with add back [70, 71] may suppress endometriosis progression and extend the duration of symptom relief.

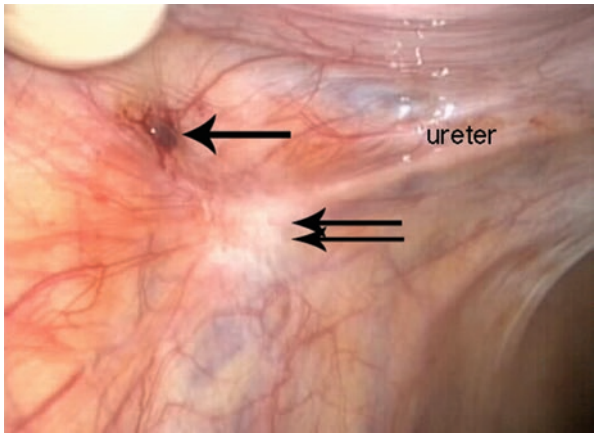


Fig. 26.12 Hemorrhagic endometriosis (arrow) involving the left pelvic sidewall with an atypical white fibrotic endometriosis lesion (double arrow) immediately over the left ureter and left ovarian fossa in a 16-year-old patient with stage II endometriosis

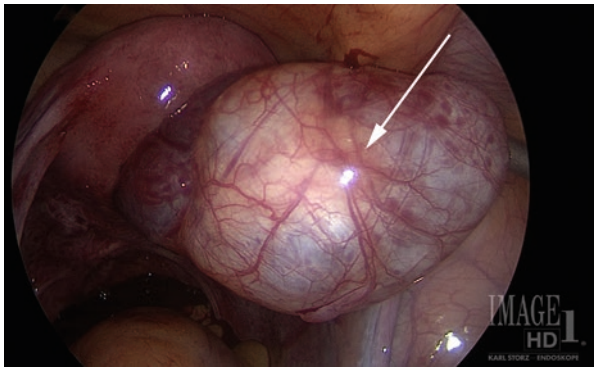


Fig. 26.13 Intraoperative laparoscopic view of an approximately 8-week right tubal pregnancy, unruptured

Fallopian Tube Masses

Pregnancy-Related Adnexal Masses

Adolescents who have secondary amenorrhea, pain, vaginal bleeding, and are sexually active should be evaluated for pregnancy and ectopic pregnancy [72]. Ectopic pregnancy accounts for approximately 2% of all pregnancies, and the fallopian tube is the most common location of implantation accounting for 90% of cases [73]. Implantations in the abdomen (1%), cervix (1%), ovary (1–3%), and cesarean scar (1–3%) are less common but incur more morbidity and mortality [74]. Assessment and treatment are similar to adults: if hemodynamically unstable or unable to comply with the medical management protocol, then surgical management is performed. If hemodynamically stable and able to comply with the follow-up protocol, unruptured ectopic pregnancies (Fig. 26.13) in adolescent patients can be successfully treated with methotrexate with the same protocol as adults. In a study comparing adolescents and adults with an ectopic pregnancy, 85% did not require surgical intervention after methotrexate. Surgical intervention rates were slightly higher, and success rates are slightly lower for adolescent patients, but the differences were not statistically significant ($p = 0.71$) [75].

Paratubal and Paraovarian Cysts

Paratubal cysts known interchangeably as paraovarian cysts constitute about 10% of adnexal masses in the general female population [76] and 7.3% in the pediatric and adolescent population [77]. They are located in the broad ligament between the ovary and fallopian tube. The cysts are usually benign and originate from the mesothelium that covers the peritoneum, the Müllerian (paramesonephric), or the Wolffian (mesonephric) ducts. Paramesonephric duct remnants tend to occur more commonly within the broad ligament than the fimbriated ends of the fallopian tube. When a cyst is pedunculated, small (<2 cm), often multiple, and located near the fimbria of the fallopian tube, it is referred to as a hydatid cyst of Morgagni (Fig. 26.14), a specific variant of the paratubal cyst. Smaller cysts are asymptomatic and usually are incidental findings. The average size cyst is 1–8 cm [78]. However, larger "giant" cysts (Fig. 26.15) can hemorrhage, rupture, or twist and cause pain. Giant paratubal cysts greater than 10 cm in diameter are unusual [79]. Torsion may involve only the cyst itself or the cyst and adjacent structures including the fallopian tube broad ligament or ovary.

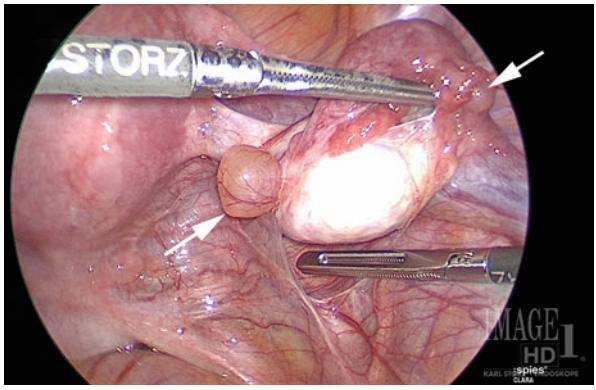


Fig. 26.14 A small paratubal cyst (arrow) of the right ovary. Paratubal cysts are also called paraovarian cysts. These particular cysts (arrows) are small, located at the fimbriae; thus are hydatid cysts of Morgagni

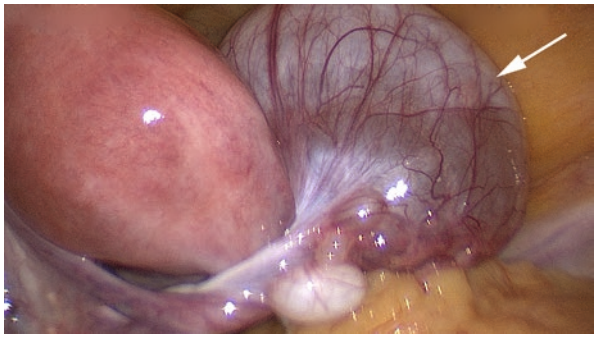


Fig. 26.15 Rarely paratubal cysts can enlarge and become giant paratubal cysts as in this case where the weight of the enlarged left paratubal cyst (arrow) pulls the left adnexa across the pelvis into the anterior aspect of the right adnexa

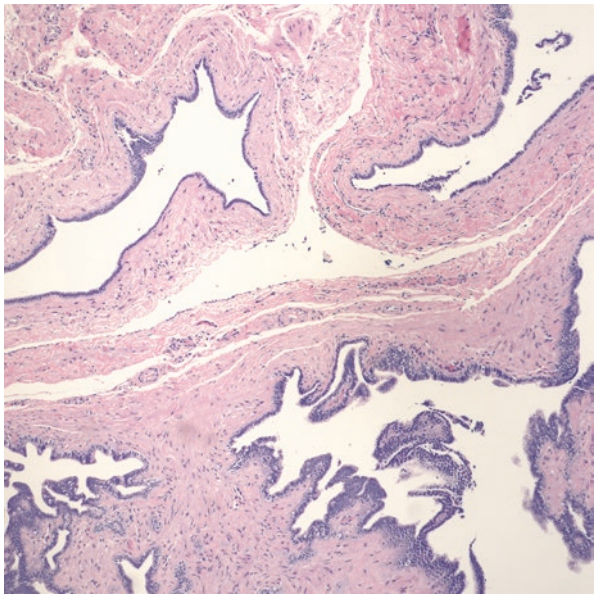


Fig. 26.16 Paratubal cyst magnified at 10×. Paratubal cyst with simple, serous lining and no associated complexity or atypia

The preoperative differentiation between paratubal and ovarian cysts is difficult to establish because of the close proximity of the ovary, fallopian tube, and cysts. Preoperative ultrasonography correctly predicted separate paratubal cysts in only 6.6% of surgical cases [76]. Histologically paratubal cysts are simple cysts filled with serous fluid (Fig. 26.16). Malignancy is rare. If papillary excrescences on the internal wall are present and the size is greater than 5 cm, there is an increased risk of malignancy [80]. Treatment is removal, preferably via a minimally invasive technique.

Infection and Sequelae of Inflammation

Less common in pediatric and adolescent populations are pelvic infections. Fever, leukocytosis, abdominal and pelvic pain, and pelvic mass on examination or imaging are suggestive of an acute inflammatory process such as pelvic inflammatory disease (PID). Specifically, PID is an infection of the upper genital tract, including endometritis, salpingitis, oophoritis, peritonitis, perihepatitis, and tubo-ovarian abscess (TOA). Among virginal adolescent females, PID and TOA are extremely rare with only a few case reports due to primarily *Escherichia coli* infections. The proposed mechanism describes pooling of urine in the vagina secondary to obesity and a recessed urethra and concurrent urinary tract infection [81]. Sexually active adolescents are at increased risk for developing PID and TOA compared to older women [82]. Physiologically, adolescents are thought to have an increased susceptibility because the immature cervix has a larger proportion of columnar epithelium

on the ectocervix (ectropy) and offers a larger surface area for microorganisms to adhere and colonize [83]. PIDs are typically polymicrobial infections including *Chlamydia trachomatis*, *Neisseria gonorrhea*, endogenous vaginal flora, genital mycoplasma, and *Mycobacterium tuberculosis* bacilli (TB). In developing countries where there is a high prevalence of TB, genital TB infection is a common cause of pelvic infection. TB reaches the genital tract by hematogenous spread from the lungs. Genital TB has subclinical symptoms, and almost it always affects the fallopian tubes (95–100%) and uterine endometrium (50–60%), causing scarring and infertility [84].

Clinical diagnosis of PID is imprecise, and the CDC supports the use of minimum criteria and additional supportive criteria (Table 26.5). Imaging with ultrasound can assist with the diagnosis of PID and rule out other pelvic pathologies. Thickened, inflamed (salpingitis), fluid-filled (hydrosalpinx), or pus-filled (pyosalpinx) fallopian tubes are highly suggestive of PID. Progressive PID can become an inflammatory mass involving the fallopian tube, ovary, and other adjacent organs such as the bowel and bladder called a tubo-ovarian complex, or a collection of pus called TOA. CT is preferred when gastrointestinal pathologies are also being considered. CT scan can identify tubo-ovarian complexes or TOA appearing as rim-enhancing adnexal masses, adjacent bowel thickening, mesenteric stranding, and free pelvic fluid. Depending on severity, treatment consists of oral antibiotics or intravenous antibiotics and hospitalization, and in extreme cases surgical intervention may be necessary. Late sequelae of PID are pelvic adhesions (Fig. 26.17a), hydrosalpinx, Fitz-Hugh–Curtis syndrome or perihepatitis and perihepatic adhesions (Fig. 26.17b), and peritoneal inclusion cysts.

Table 26.5 Minimum and supportive criteria for diagnosing PID [82]

One or more of the following minimum clinical criteria are present on pelvic examination to diagnose PID
Cervical motion tenderness or
Uterine tenderness or
Adnexal tenderness
One or more of the following additional criteria enhance the specificity
Oral temperature >101 °F (>38.3 °C)
Abnormal cervical mucopurulent discharge or cervical friability
Presence of abundant numbers of WBC on saline microscopy of vaginal fluid
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Laboratory documentation of cervical infection with *N. gonorrhea* or *C. trachomatis*
The most specific criteria for diagnosing PID
Endometrial biopsy with histopathologic evidence of endometritis
Transvaginal US or MRI techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
Laparoscopic findings consistent with PID

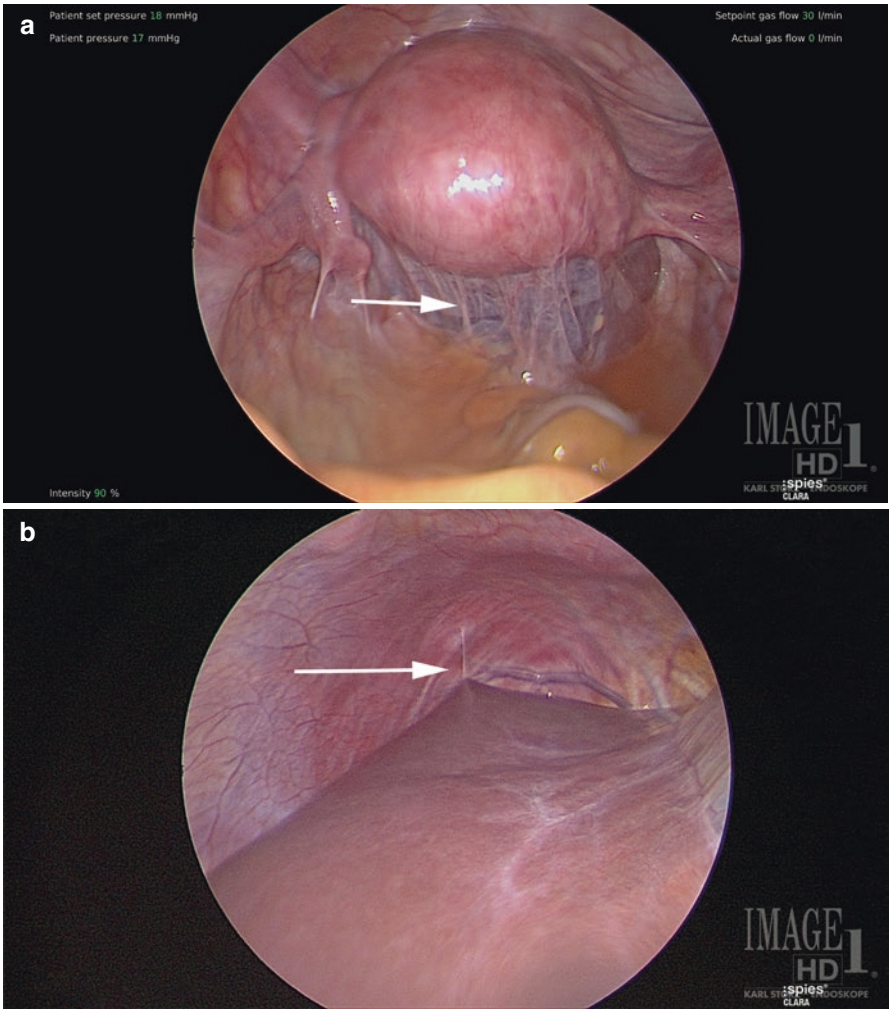


Fig. 26.17 (**a**) The same patient with dense pelvic adhesions blanketing the uterus and adnexa. (**b**) Perihepatic adhesions (arrow) or Fitz-Hugh–Curtis syndrome in a patient with prior history of chlamydia and pelvic inflammatory disease

Uterine Masses

Leiomyomas

Pedunculated, subserosal leiomyomas or fibroids located in the broad ligament or in a lateral position (Fig. 26.18) can mimic adnexal masses on ultrasound and some CT imaging. If transvaginal ultrasound is indeterminate, MRI imaging may be able to better differentiate between the soft-tissue organs of the pelvis [85].

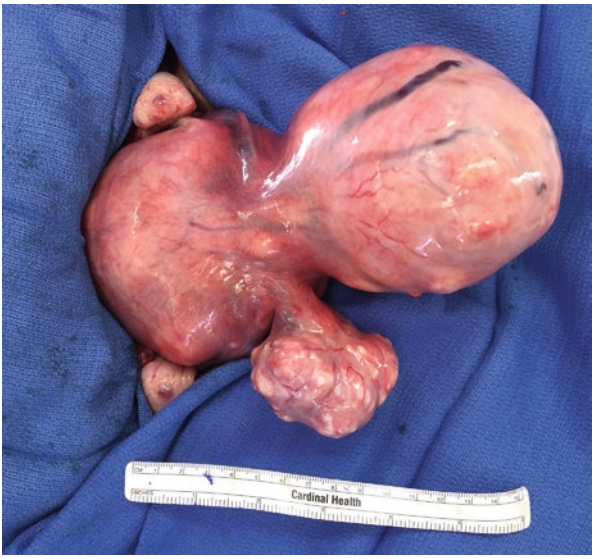


Fig. 26.18 Pedunculated leiomyomas can be interpreted on physical exam or ultrasound imaging as adnexal masses. MRI imaging can usually differentiate leiomyomas from adnexal masses if other imaging is indeterminate

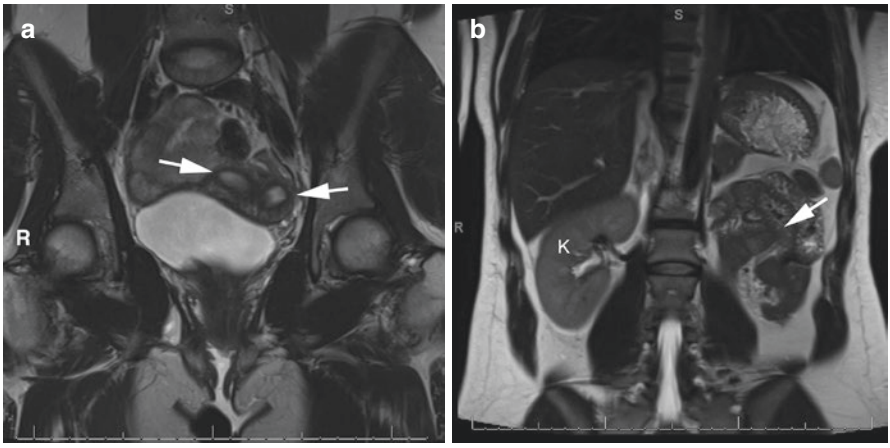


Fig. 26.19 Uterus didelphys with a nonobstructed hemivagina. (**a**) Coronal T2-weighted MR image shows widely separated horns of a uterus didelphys (arrows). (**b**) Coronal T2-weighted image, note the absent left kidney (arrow) with bowel in the renal fossa. K = normal right kidney

Müllerian Anomalies

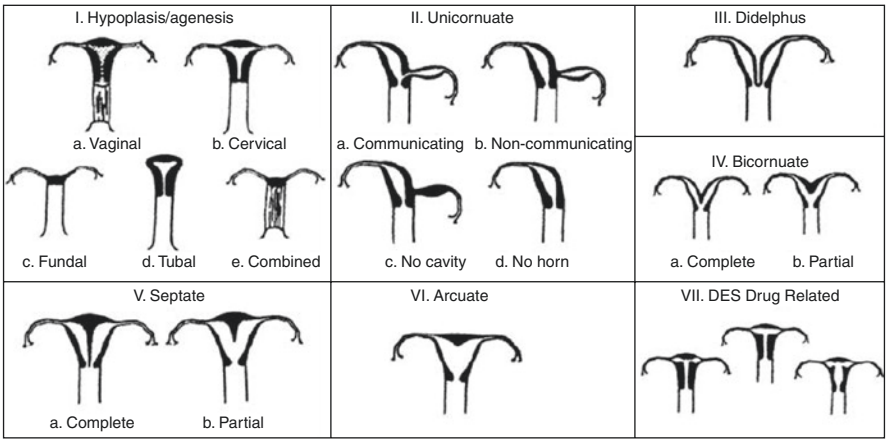
Congenital anomalies of the female reproductive tract occur 1 in 200 (0.50%) women. Uterine anomalies are identified in 1 in 600 (0.17%) fertile women and 1 in 30 (3.5%) infertile women. The distribution of Müllerian anomalies (Table 26.5) is approximately 7% arcuate, 34% bicornuate, 11% didelphys (Fig. 26.19a), 5% unicornuate, and 4% hypoplastic/aplastic/sold [86]. Normal development of the female

reproductive tract requires a series of events: Müllerian duct migration, elongation, fusion, canalization, and septal resorption. The fused caudal portion of the Müllerian ducts becomes the uterus and upper 80% of the vagina, and the unfused cephalad portion becomes the fallopian tubes. Failure of any part of this process can result in a congenital anomaly with and without obstruction. Since Müllerian development occurs in association with the urinary tract, anomalies of the kidney and ureter are commonly identified. Upper urinary tract abnormalities include renal anomalies (20–30%), such as a horseshoe, pelvic kidney, renal agenesis (Fig. 26.19b), duplication of the collecting system, and ectopic ureters [87]. In over 50% of the time, renal agenesis is predictive of an obstructive ipsilateral Müllerian anomaly [88]. Adolescents may present with cyclic or noncyclic pelvic pain and dysmenorrhea suggestive of retrograde menstruation, endometriosis, or an obstructive anomaly. Primary amenorrhea with pelvic, vaginal, back pain, and a pelvic mass is indicative of a transverse vaginal septum or imperforate hymen. MRI of the pelvis and abdomen is considered the standard imaging technique for diagnosing suspected Müllerian and associated renal anomalies, as it is both sensitive (100%) and specific (80%) [89] (Table 26.6).

Imperforate Hymen

Imperforate hymen (IH) is a rare congenital anomaly of the female genital tract, in which the hymen completely obstructs the vaginal opening. It occurs in about 1 in 2000 females [90]. IH is typically not related to Müllerian anomalies, and additional workup of urogenital anomalies is unnecessary. Developmentally, the lower vagina forms from urogenital sinus epithelium. Adolescents present with primary amenorrhea, and a bulging, bluish hymenal membrane is observed on physical exam.

Table 26.6 ASRM Müllerian anomalies classification [102]



Abdominal ultrasound may show a cystic pelvic mass. Treatment is cruciate incision or excision of the hymen. Without management, IH can cause infections, subfertility, endometriosis, and hydronephrosis and renal failure in extreme cases [91].

Nongynecologic Benign Adnexal Masses

The abdomen and pelvis contain viscera of several organ systems. Although gynecologic processes are primarily responsible for adnexal masses in females, consideration must be given to masses arising from the urogenital and gastrointestinal tracts.

Benign masses arising from the urogenital tract include a pelvic or ectopic kidney, urachal abnormalities, ureteral diverticulum, bladder diverticulum, and Gartner's duct cyst. Kidney development begins during the sixth to eighth weeks of life. Failure of ascent of the kidney results in the kidney remaining in the pelvis. In very rare cases, a pelvic cake kidney is described consisting of a single lump of fused renal parenchyma, draining via two separate ureters and less commonly a single ureter, and is associated with Müllerian anomalies [92]. In most cases pelvic kidneys are asymptomatic. They are typically detected incidentally or in the work of pelvic pain or recurrent urinary tract infections [93]. Urachal abnormalities arise when the urachus, an embryological remnant of the allantois, fails to narrow into a fibromuscular strand. This strand is typically extending from the apex of the bladder to the umbilicus, and it lies between the extraperitoneal space of Retzius between the transversalis fascia anteriorly and the peritoneum posteriorly. Incomplete involution during development results in four main types of urachal abnormalities presenting as midline supravesical soft-tissue mass on imaging: (1) patent urachus or urachal fistula, (2) umbilical-urachal sinus, (3) vesicourachal diverticulum, and (4) urachal cyst [94]. Female urethral diverticulum is uncommon, benign epithelium-lined outpouchings of the urethra commonly presenting with urinary incontinence and recurrent urinary tract infections [95]. Bladder diverticulum is a large herniation of the bladder urothelium through the muscularis propria of the bladder wall. Congenital diverticula present during adolescence with a peak incidence of 10 years and are usually solitary and located lateral and posterior to the ureteral orifice. The primary cause is thought to be a congenital weakness of the detrusor muscle at the level of the ureterovesical junction with or without coexisting lower urinary tract abnormalities [96]. A mesonephric cyst (Gartner's duct cyst) is a benign vaginal cystic structure that arises from the vestigial remnant of the mesonephric (Wolffian) duct, which, during male embryogenesis, from the seminal vesicles, vas deferens, and epididymis. Gartner's ducts (Fig. 26.20) are paired structures on either side of the urethra; when cysts become large, they can appear as midline pelvic and vaginal masses [97].

Benign adnexal masses of gastrointestinal origin among children and adolescents include Meckel's diverticulum, appendiceal abscesses, appendiceal mucocele, and CRC due to hereditary syndromes. Meckel's diverticulum is the most common congenital abnormality of the gastrointestinal tract. The anomaly is due to incomplete

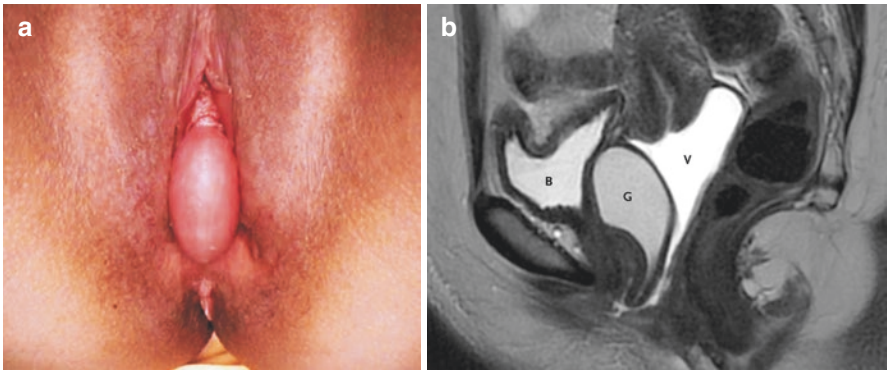


Fig. 26.20 Gartner's duct cyst. (**a**) A smooth, nontender mass 5 cm in diameter, in the midline anterior wall of the vagina. No pelvic organ prolapse was present. A cystoscopic exam did not reveal a urethral or bladder diverticulum. (**b**) Sagittal T2-weighted MR image with contrast medium in the vagina reveals the Gartner's duct cyst (G) between the bladder (B) and the vagina (V). (Image from Hoogendam et al. [97])

obliteration of the omphalomesenteric duct during the seventh week of development [98]. The condition was thought to affect 2% of the population, with 2% developing complications, the majority present before the age of 2, and the diverticulum is classically located 2 feet proximal to the ileocecal valve; hence, the "rule of 2s" [99]. Mostly asymptomatic, Meckel's diverticulum can be a source of bleeding, infection, perforation, volvulus, or intussusception leading to obstruction, and it is frequently misdiagnosed as appendicitis. Appendicitis is the most common childhood and adolescent surgical emergency. Appendiceal phlegmon and abscess account for 2–10% of acute appendicitis and can present with imaging findings of an infected pelvic mass [100]. Appendiceal mucoceles are a catchall term for benign and malignant lesions and are subdivided by WHO classification into (1) simple mucocele which is the appendiceal dilation with accumulation of mucus due to obstruction of the lumen, (2) cystadenoma which is a dilated, mucus-filled appendix containing adenomatous mucosa, and (3) cystadenocarcinoma with adenocarcinoma associated with dilated, mucus-filled appendix. The hereditary syndromes HNPCC and FAP are associated with onset of early CRC, with a mean age of diagnosis of 45 years. Those with FAP develop polyposis in adolescents with progression to CRC by middle age. Surveillance among patients with hereditary CRC syndromes is recommended to start early screening with colonoscopy, and prophylactic colectomy in cases of FAP [6].

Summary

Adnexal masses in the pediatric and adolescent population may have a broad differential. Though most pathologies concern the ovaries, consideration should be given to other gynecologic and nongynecologic structures in the abdomen and

pelvis. Ultrasound is the preferred initial diagnostic imaging modality because it is a nonionizing form of radiation and safer for younger patients. If ultrasound is non-diagnostic, then CT or MRI can be employed judiciously. For ovarian masses that pose a risk of malignancy, serum tumor markers can assist in narrowing down the differential diagnosis. Medical and surgical treatment should focus on fertility-sparing, minimally invasive techniques that balance conservation of the female reproductive organs with removing the pathology.

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Chapter 27
Adnexal Masses in the Adolescent Population

Vanessa Martinelli, Laura Mucenski, Roseanna Miller, and Farr Nezhat

Introduction

The increased use of ultrasound for the diagnosis of abdominal and pelvic pain has led to the increased diagnosis of adnexal masses. In adolescents, adnexal pathology most commonly originates from the ovary, but it can also be caused by tubal pathology such as paratubal cysts, and occasionally from the uterus such as uterine fibroids or congenital anomalies. On rare occasions, gastrointestinal pathology such as bowel or appendiceal tumors or dilated bowel loops may be mistaken for an adnexal mass (Fig. 27.1). For the majority of adolescent patients, these masses are found during workup for abdominal and pelvic pain secondary to hemorrhagic cyst rupture or ovarian torsion. Most physiologic cysts will resolve within a few months; however, most persistent adnexal masses will require further workup and possible surgical excision.

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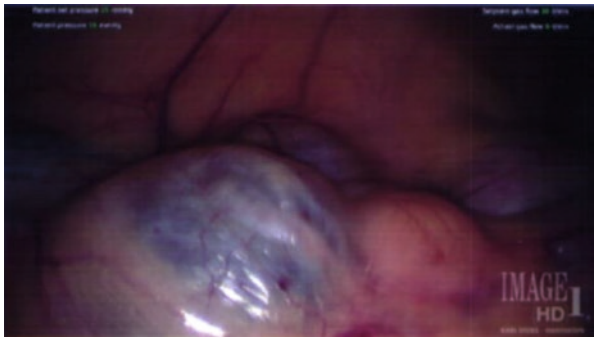

Fig. 27.1 Mesenteric mass mistaken for an adnexal cyst on ultrasound imaging

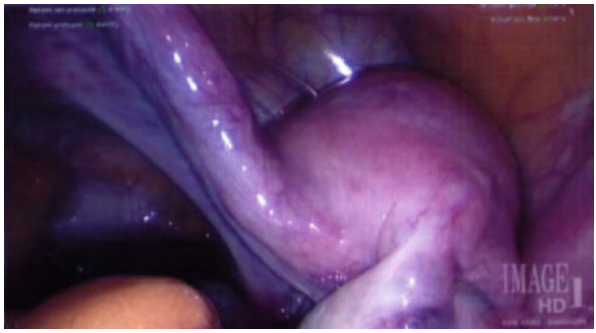

Fig. 27.2 Unicornate uterine horn noted on laparoscopy

Causes of Adnexal Pathology in Adolescence

The most common causes of adnexal pathology in adolescence are physiologic ovarian cysts. However, the differential diagnosis should also include benign ovarian masses such as dermoids, serous and mucinous cystadenomas, endometriomas, or adenofibromas [1]. Tubal pathology includes tubo-ovarian abscess, hydrosalpinx, and paratubal cysts. Uterine anomalies and fibroids, though rare in adolescence, can also appear as adnexal masses in imaging (Fig. 27.2). Even though the incidence of malignancy is low in this patient population, epithelial tumors, germ cell tumors, and sex stromal tumors should be included in the differential diagnosis.

Diagnostic Approach

Evaluation of pelvic adnexal masses should begin with a physical examination. Depending on the age, maturity, and virginal status, some patients may be able to tolerate a pelvic examination. These examinations should focus on identifying uterine, cervical, and adnexal anatomy. In addition to the examination, there should be a low threshold for obtaining a pelvic ultrasound for the evaluation of pathology [2]. While transvaginal ultrasound is better able to visualize adnexal anatomy,

abdominal ultrasound is useful especially in virginal females and those with pathology that extends outside the pelvis.

During an ultrasound examination, once a pelvic mass has been detected, the following should be noted: size, location, bilaterality, simple versus complex, nodularity, papillary projections, and free fluid (ascites) [3]. With the ability to characterize pelvic masses, studies have shown ultrasound to be a reliable tool in distinguishing between malignant versus benign etiology, with sensitivity rates between 89% and 99.7% [4].

While ultrasound is the initial imaging modularity of choice [2, 5, 6], advanced imaging techniques can be utilized to help delineate pathology. Magnetic resonance imaging (MRI) is useful to further assess uterine and adnexal structures, such as Mullerian anomalies and ovarian pathologies [2, 6, 7]. If malignancy is suspected, then a computerized tomography (CT) scan is a reliable and sensitive modality in detecting abdominal structures and detecting metastases [6].

Ultimately, if there is any doubt, diagnostic laparoscopy should be considered for proper diagnosis.

Ovarian Pathology

Simple and Hemorrhagic Cysts

The most common ovarian masses in adolescents, as with any premenopausal women, are functional cysts. During ovulation, a primordial follicle is recruited to become the dominant follicle. These can be seen prior to ovulation as a simple cyst, which presents as an anechoic cystic mass. During ovulation, it is not unusual for hemorrhage to occur inside these cysts [1]. A simple ovarian cyst usually presents as a simple anechoic adnexal mass whereas a hemorrhagic corpus luteum cyst presents as a homogeneous or complex mass (Fig. 27.3). Spanos et al. found that the majority of mobile, unilocular ovarian masses between 4 and 10 cm resolved within

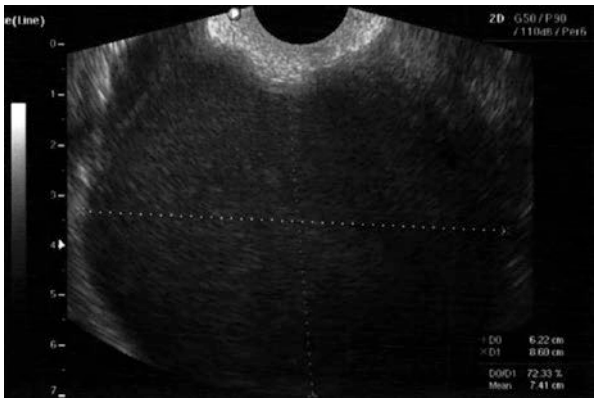

Fig. 27.3 Hemorrhagic cyst appearing as a homogenous echogenic mass on transvaginal ultrasound

6 weeks [8]. The best predictors for the non-resolution of ovarian masses are size (greater than 5 cm) and complex appearance [9].

Polycystic Ovaries

Patients with polycystic ovarian syndrome (PCOS) can develop multiple small follicles around the periphery of the ovary. These benign cysts are physiologic and the result of hormonal imbalances due to anovulatory cycles [10]. In the majority of patients, these cysts are found incidentally, as up to 23% of patients with polycystic ovaries have no other symptoms of PCOS; of those who are worked up for the disorder, the majority are asymptomatic. Rarely, a large number of cysts can cause ovarian torsion.

Leiomyomas

Uterine fibroids are a rare finding in adolescent women. These masses very commonly present as subserosal, intramural, pedunculated, or intraligamentous (Fig. 27.4). Approximately 1/3 will increase in size whereas a small percentage will undergo red/carneous degeneration secondary to hemorrhagic infarction with subsequent acute abdominal pain.

Endometrioma

Endometriosis affects roughly 10% of the female population, including adolescent girls [11–13]. It is a disease characterized by ectopic endometrial tissue, glands, and stroma that has implanted outside the uterine corpus and is associated with

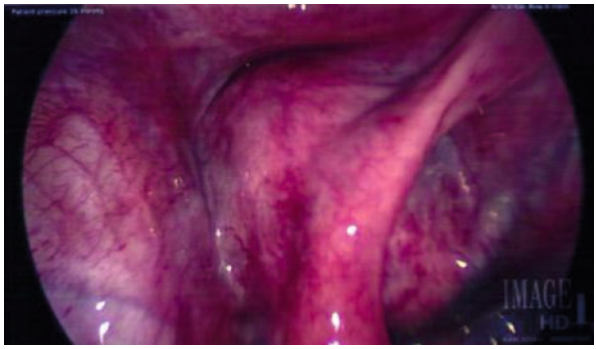

Fig. 27.4 Board ligament myoma

dysmenorrhea, chronic pelvic pain, and infertility. One of the most common locations for endometriotic implant is the ovaries. In response to these implants, ovarian endometriomas may form. The cysts are defined by the presence of ectopic endometrial tissue implanted or embedded within the ovarian cortex [2, 11]. The incidence of endometriomas in adolescent females with endometriosis ranges from 17% to 44%, similar to that of the adult population [2, 5]. The presence of endometriomas typically represents an advanced stage of endometriosis. Patients may present with complaints of dysmenorrhea and/or chronic pelvic pain and are found to have a pelvic mass on examination or imaging. Adolescents in particular may present with sudden onset pain, representing ruptured endometrioma and/or ovarian torsion. Management of these cysts depends on presenting symptoms as well as the etiology of cyst formation.

In these cases, it is recommended to proceed with surgical excision with preservation of ovarian tissue as the primary goal. Surgical management of these cysts should be undertaken with knowledge of cyst classification. According to Nezhat et al., there are two types of endometriomas: Type I and II (Figs. 27.5 and 27.6) [14]. Type I is when endometrial tissue implants on the surface of the ovary with cyst formation caused by endometrial bleeding into the cortex [11, 14]. These cysts are also called "true endometriomas" and are typically less than 5 cm in size [14]. Given its formation, no clear plane exists between type I cyst walls and ovarian

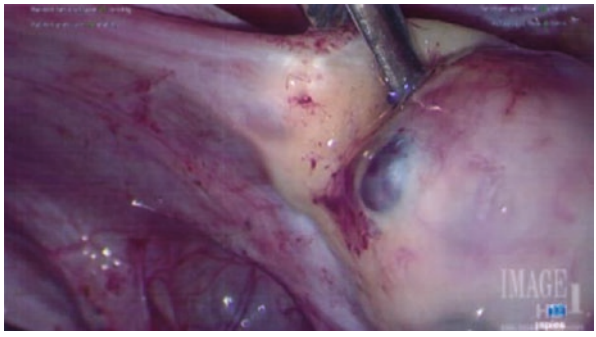

Fig. 27.5 Type I endometrioma found on the surface of the ovary during exploratory laparoscopy for dysmenorrhea

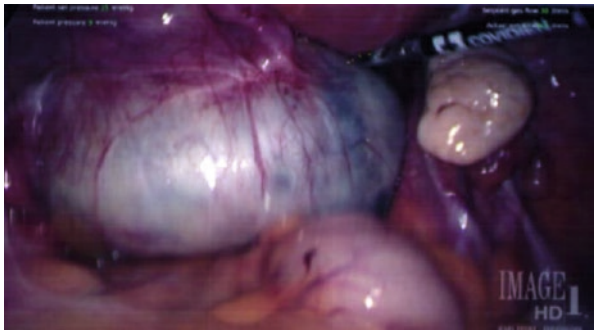

Fig. 27.6 Type II endometrioma found in the patient with stage IV endometriosis

cortex, and cysts should be removed in pieces or ablated cautiously to avoid damage to the ovary. Type II endometriomas are formed from functional cysts that are then invaded by endometrial implants. There are three subtypes of type II endometriomas: A, B, and C, based on how much endometrial tissue is involved within the functional cyst wall. Type II A cysts contain less than 10% endometrial tissue invasion and have a cyst wall that is easily separated from surrounding ovarian tissue. Type II B and C cysts contain 10–50%, and greater than 50% endometrial tissue invasion, respectively. These cysts are progressively more difficult to separate from ovarian tissue, and, in the case of Type II C cysts, may be adhered to surrounding structures secondary to fibrosis [11]. Given these cystic characteristics, surgeons must take care to completely separate a cyst from ovarian tissue with minimal damage to the ovarian cortex and hence ovarian reserve. If complete excision is not possible, due to dense adhesions, the ablation of the cyst wall can be utilized [11].

Post-surgery, and in cases in which surgical intervention is not feasible, medical management with hormonal suppression is recommended for control of disease reoccurrence and progression [2].

Pediatric Neoplasms

Ovarian tumors in the pediatric and adolescent population are very rare and represent approximately 1% of childhood cancer [15]. They are the most common gynecological neoplasm of childhood. An acute abdomen or signs of precocious puberty in a pediatric patient should prompt an evaluation of the adnexa. These tumors differ histologically and fall in the category of germ cell, sex cord stromal, and epithelial. They may be benign or malignant and often contain cystic components. Solid components are the most statistically significant predictor of malignancy [16]. Special consideration must be taken in the pediatric and adolescent population when considering ovarian surgery due to the potential for fertility compromise, whether from direct ovarian trauma or adhesion formation [17]. The International Federation of Gynecology and Obstetrics staging system is used, similarly to adult ovarian tumors.

Germ Cell Tumors

The most common neoplasm in children and adolescents are germ cell tumors, and the most common germ cell tumor is a teratoma [18]. These tumors are histologically diverse and contain tissue derived from 2 of 3 germ cell layers (ectoderm, endoderm, and mesoderm). They often contain elements such as skin, fat, teeth, hair, cartilage, and bone; the presence of cutaneous elements gives these tumors the name “dermoid” [18]. Most of these tumors are benign however rarely they may

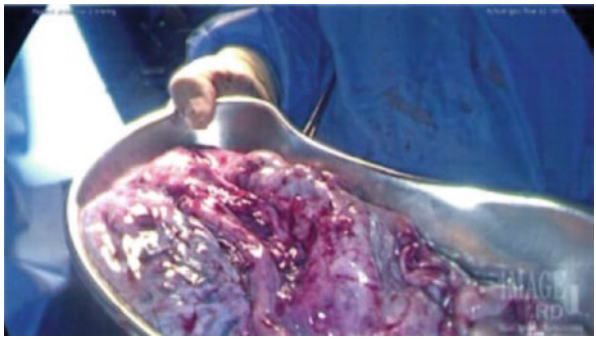

Fig. 27.7 Enlarged 30 cm complex adnexal mass found to have immature teratoma

undergo a malignant transformation (Fig. 27.7). This usually occurs later in life and they usually degenerate to squamous cell carcinoma. Monodermal teratomas, with a predominance of one cell line tissue type, have been reported in children as well and are usually neural, thyroid, or carcinoid in nature [18]. On imaging, teratomas will have calcifications or fat present and a dermoid plug may be seen, termed Rokitansky nodule. Elevations of AFP and βHCG on serum blood work may indicate malignant transformation. In the past, teratomas were removed by performing a traditional laparotomy, but advances in minimally invasive surgery have made laparoscopic approaches more popular [19, 20]. Care must be taken to remove the cyst intact to avoid cyst rupture or spillage, which is more likely when the cyst measures greater than 5cm [21]. If intra-abdominal rupture occurs, copious irrigation of the peritoneal cavity must be performed to prevent chemical peritonitis.

Rare tumors such as gonadoblastomas are associated with gonadal dysgenesis, and patients may have a chromosomal abnormality. These tumors are often diagnosed at the time of evaluation for delayed puberty or menarche, and do not generally present with a mass or pain. Recently, two cases of hypercalcemia in adolescents presenting with a large pelvic mass found to be dysgerminomas have been reported [22]. Dysgerminomas are the most common malignant germ cell tumor of the ovary and may occur bilaterally in up to 30% of cases [18]. Dysgerminomas are derived from the primordial germ cells of the sexually undifferentiated gonad and are histologically identical to seminoma of the testes. Yolk sac tumors (formerly referred to as endodermal sinus tumors) are the second most common malignant germ cell tumor of the ovary and cause an elevated in serum AFP. When elevated, AFP levels may be used to monitor treatment response and for post-treatment surveillance [23]. Abdominal enlargement is the most common complaint among patients diagnosed with yolk sac tumors; however, presenting symptoms of virilization have been reported when Leydig cells were present in tumor stroma [24].

In terms of treatment, Stage 1a dysgerminoma and grade 1, stage 1 immature teratomas may be observed after adequate surgical therapy; however, all other germ cell tumors require chemotherapy to decrease the risk of recurrent disease [18].

Sex Cord Stromal Tumors

In rare cases, patients found to have hydrothorax and nonmalignant ascites should be worked up for Meigs syndrome; thecomas, fibromas, or granulosa cell tumors of the ovary may be present. Fibromas and thecomas are most commonly seen in older patients and account for a very small number of tumors in the pediatric population. Basal cell nevus syndrome (Gorlin syndrome) may predispose patients to ovarian fibromas and are caused by a mutation in the Ptch gene [15]. Fibromas may cause an elevated CA-125 which may initially raise concern for malignancy in these benign tumors. Thecomas may contain lutein cells, known as luteinized thecomas, and may produce estrogenic and androgenic hormones, which may be associated with sclerosing peritonitis. Fertility sparing treatments in these patients are standard of care because of these benign features.

Juvenile granulosa cell tumors (JGCT) are very different than their adult-type counterparts and comprise 5% of all granulosa cell tumors [25]. They tend to have a higher proliferative rate, however a lower risk for late recurrence. Inhibin and Mullerian inhibitory substances may be elevated in these patients; however, more studies are needed to evaluate the use of these markers in the pediatric population [26]. They present up to 90% of the time with isosexual precocious puberty secondary to estradiol production; however, rarely they are associated with androgenic manifestation [27]. These tumors may be associated with congenital syndromes such as Ollier's syndrome and Malfucci syndrome, which are subtypes of enchondromatosis syndromes involving the skeletal system [27]. Call-Exner bodies and coffee-bean grooved nuclei are not frequently seen as in the adult subtype [15]. Stage 1 JCGT is often the diagnosis at presentation; however, they can have malignant potential. Treatment is geared to the stage and long-term follow up is required, including pelvic imaging and estradiol levels.

Patients who present with signs of androgen excess, including hirsutism, deepening voice, and amenorrhea, should be evaluated for Sertoli–Leydig tumors, a very rare subtype of sex cord stromal neoplasms. Serum testosterone may be elevated in these cases, leading to the hormonally mediated symptoms. These tumors are generally unilateral and contained to the ovary. Sertoli and Leydig cells are present in different proportions and tumors are categorized into moderately and poorly differentiated forms, ultimately correlating to prognosis [27]. Fertility-sparing surgery is often pursued unless bilateral ovarian disease or advanced-stage disease is present.

Epithelial Tumors

Benign epithelial tumors such as serous, mucinous, and endometroid cystadenomas are more common in older women but comprise up to 28% of pediatric adnexal masses (Figs. 27.8 and 27.9). Malignancy rates are high in epithelial tumors and

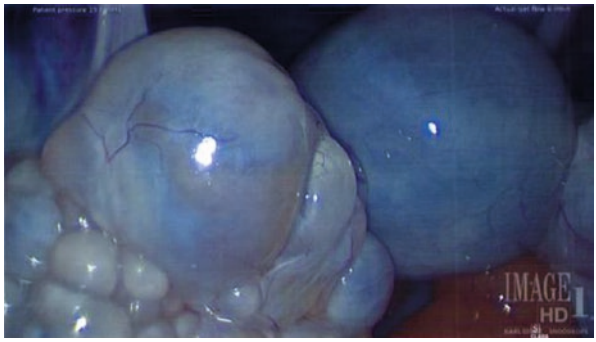

Fig. 27.8 Multi-cystic serous cysts found to be serous cystadenocarcinoma on final pathology

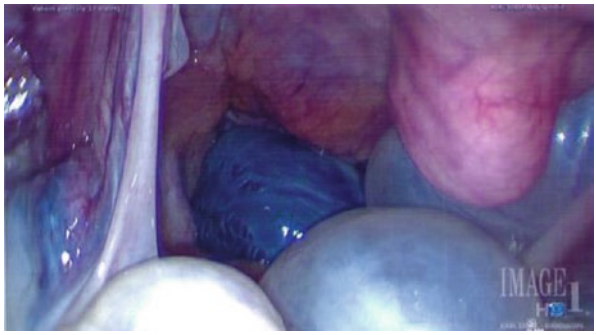

Fig. 27.9 Multi-cystic serous cysts found to be serous cystadenocarcinoma on final pathology

tumor markers, such as CA-125 and CA 19–9, may be elevated. Any suspicion for malignancy should be evaluated surgically with pelvic washings, cystectomy, peritoneal, omental and contralateral ovarian inspection, and biopsies of suspicious areas. Borderline or "low malignant potential" tumors account for 40% of epithelial tumors where malignant neoplasms represent 5–16% [15]. Pediatric patients are treated similarly to adults, with surgery and chemotherapy when indicated. Fertility sparing surgery is not recommended for patients with stage II or higher disease.

Management

Management of adolescent adnexal masses is largely dependent on the patient's symptomatology and tumor characteristics. In this age group, conservative management should be the ultimate goal both medically and surgically. When deciding between medical versus surgical interventions, the decision should be made based on the whole clinical picture and in collaboration with the patient and her family.

Medical Intervention

Medical therapy with close surveillance and/or hormonal suppression can be an appropriate option for certain clinical situations. Adnexal masses that are found incidentally, in asymptomatic patients, and are less than 5 cm in size with no signs of solid components or malignancy on imaging, can be managed with close observation [5]. In this subset of patients, pelvic ultrasound can be used to monitor the mass size and characteristics every 3–4 months. In addition to observation, hormonal suppression with combined oral contraceptive pills can be utilized to suppress ovarian ovulation. Persistence of the adnexal mass, increase in size, or change in characteristics are reasons to proceed from medical to surgical intervention [6].

Surgical Intervention

Surgical management for adnexal masses in the adolescent population is an important intervention for select patients, as in the adult population. Within this age group, there can be hesitance among providers in proceeding with surgery. While surgery in the adolescent population must be undertaken with great care by skilled surgeons, certain clinical findings merit surgical intervention. Patients that are symptomatic from adnexal masses must be significantly worked up as previously discussed. Gynecologic emergencies, such as torsion, ectopic pregnancy, and ruptured hemorrhagic cyst, warrant immediate surgical intervention [5].

Lesions suspicious for malignancy, persistent and/or enlarging endometriomas, and dermoid cysts, also warrant surgical intervention. The primary goal of surgery in adolescents is the conservation of fertility and if possible of both ovaries and fallopian tubes. Studies have shown that the presence of a gynecologic surgeon increases the chance of ovarian preservation during surgery in adolescent patients compared to pediatric surgeons operating alone [14]. In unique cases suggestive of malignancy, frozen pathological section can be an invaluable tool in helping determine the need for further procedures, such as unilateral oophorectomy. It is important to note, however, that the accuracy of frozen section decreases with tumor size [5]. Thus, if any doubt exists on the malignant nature of a mass, further surgical intervention should be postponed until the final pathology.

Conclusion

The increased use of ultrasound for the diagnosis of abdominal and pelvic pain has led to the increased diagnosis of adnexal masses. The physician, therefore, must be familiar with both the diagnosis and management of adnexal masses. MRI and CT scan are imaging modalities which can also be employed to better characterize these

masses and evaluate for non-gynecologic pathology; however, transvaginal and transabdominal ultrasound should be the first modality used. Observation of asymptomatic, small adnexal masses is a viable option in the adolescent patient. However, for larger, complex, or persistent masses, or in the case of an acute abdomen concerning ovarian torsion or cyst rupture, surgical intervention is recommended. With the advancement in new technology and increased number of minimally invasive trained gynecologic surgeons, we believe that most surgical procedures for this condition should start with diagnostic laparoscopy. Given the benefits of minimally invasive surgery, laparoscopy by a skilled laparoscopic surgeon should be preferred to laparotomy for surgical management.

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Chapter 28
Ovarian Torsion in Adolescents

Kathryn C. Stambough and Krista J. Childress

Introduction

Adnexal torsion, although an infrequent gynecologic condition, is one of the most common surgical emergencies of the female reproductive tract. The ovary, fallopian tube, or both adnexal structures can be involved, and symptoms result from torsion obstructing vascular supply. It is most commonly seen in reproductive-aged females, although it can occur throughout a woman's lifespan, including in-utero, premenarchal, and postmenopausal [1]. Conditions which place the adnexa at increased risk for torsion include adnexal and tubal pathology such as ovarian or tubal cysts and increased mobility of the adnexal structures due to an elongated fallopian tube, mesosalpinx, or meso-ovarium [2, 3]. Endometriosis is a risk factor for torsion, particularly from ovarian pathology due to an endometrioma or tubal pathology from adhesive disease. Adnexal torsion is a surgical emergency, given that compromise to the vascular supply leads to necrosis and potential loss of ovarian function [4–6].

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Epidemiology

Adnexal torsion is the fifth most common gynecologic emergency. The incidence of adnexal torsion in children presenting with acute abdominal pain is estimated to be 2.7%. However, adnexal torsion is likely under-diagnosed due to symptom overlap with other more common conditions [2, 7]. A systematic review of adnexal torsion in the pediatric population reported a mean age of presentation of 11.6 years in menarchal girls, accounting for 56.6% of cases [8]. The fallopian tube and the ovary more commonly concurrently twist on their vascular supply, while isolated torsion of the ovary or the fallopian tube is relatively rare [9]. Although bilateral cases of adnexal torsion have been reported, adnexal torsion usually occurs unilaterally [10–12]. Synchronous bilateral adnexal torsion, which is torsion of both adnexa simultaneously, is exceedingly rare. Asynchronous ovarian torsion, which is torsion of both adnexa but each at different time points, occurs in approximately 5% of cases [13, 14]. Asynchronous bilateral adnexal torsion may be more common if the initial episode of torsion involved normal adnexa in the absence of ovarian or tubal pathology [13].

Adnexal torsion most commonly involves the right adnexa with a ratio of 3:2. This discrepancy in laterality is attributed to the hyper-mobility of the cecum and ileum in the right pelvis, allowing more space for the right adnexa to undergo torsion compared to the smaller space allowed by the fixed sigmoid colon filling the left pelvis [15–17]. Furthermore, presentation with right lower quadrant pain and assessment for the more common condition of appendicitis may lead to a higher detection rate [17]. While adnexal torsion is more common in menarchal females and usually involves an adnexal mass, torsion in premenarchal girls more commonly involves ovaries of normal size without underlying pathology [15, 18]. Several case series have shown that up to 71% of torsion cases in premenarchal girls have normal ovarian size [19–22] and this population also has a higher recurrence rate in up to 35% of cases [22].

Endometriosis is a rare finding in premenarchal patients and therefore is a more common cause of adnexal torsion in menarchal reproductive aged females. Endometriosis is estimated to affect approximately 7–10% of women and increases with increasing age, with a prevalence of up to 50% in adolescents with severe dysmenorrhea [23, 24]. The reports of endometriosis associated with adolescent adnexal torsion in the literature are limited to only case reports or case series with small numbers. In a series of 128 cases of adnexal torsion, Hibbard documented two cases secondary to an ovarian endometrioma [7]. In a retrospective review of 245 cases of adnexal torsion at a single institution, Adeyemi et al. found no cases of torsion associated with endometriosis [10].

Pathophysiology

Torsion of the adnexa occurs when excessive rotation of the ovary, fallopian tube, or both on the underlying vascular supply leads to obstruction of blood flow [25, 26]. Due to the higher compressibility of veins, venous flow is compromised prior to

arterial flow. Venous congestion leads to ovarian tissue edema which subsequently compromises arterial flow and tissue necrosis [9]. Torsion of the adnexa usually occurs due to underlying adnexal or tubal pathology, most commonly associated with benign ovarian lesions including functional cysts, mature cystic teratomas, tubal pathology including paratubal, paraovarian cysts or hydrosalpinx [7, 10]. Malignant lesions may be associated with torsion in up to 2% of patients [10, 18, 27]. Multiple studies have demonstrated an increased risk of torsion when lesions are over 5 cm [21, 28–30]. Endometriosis affects the fallopian tube in 6% of patients and adhesions of the fallopian tubes have been demonstrated in up to 26% of these patients [31]. Although underlying inflammation and subsequent adhesive disease secondary to endometriosis may make the adnexa less likely to twist, endometriomas and abnormalities of the fallopian tube due to adhesive disease such as hydrosalpinx, are risk factors for torsion. Multiple case reports have documented isolated tubal torsion due to a tubal endometrioma, some with associated adhesions and some without [32–37].

Clinical Presentation and Diagnosis

The clinical diagnosis of adnexal torsion can be challenging given the non-specific presentation and similarities to other diagnoses that cause abdominal and pelvic pain. A systematic review reported that the most common presenting symptom of torsion, abdominal pain, was present in 97.5% of all studies reviewed [8]. The pain can be variable in nature, including acute and sharp, intermittent or constant, mild or severe, gradually increasing, and days or months in length, given that torsion can be complete, incomplete, or intermittent in nature [19, 38–40]. The characteristic pain usually presents unilaterally in the lower abdomen or pelvis. Pain that waxes and wanes may indicate intermittent torsion when the adnexa twists but then spontaneously untwists [41]. Nausea and vomiting and anorexia are also classic symptoms in confirmed cases of adnexal torsion. Most patients with torsion usually present within 72 hours of symptom onset [8, 17, 19, 42–45].

Physical examination is usually notable for abdominal pain with possible peritoneal signs including rebound and guarding. A palpable abdominal mass may not necessarily be present. Pelvic exam and/or bimanual exam is rarely indicated in the pediatric and adolescent population unless sexually active or with a vaginal complaint. However, if a pelvic exam is performed, a palpable tender mass on the affected adnexal side may be present. Although no laboratory values have been proven to assist with establishing the diagnosis of torsion, women can present with low-grade fever and leukocytosis on complete blood count due to tissue necrosis and inflammatory reaction caused by prolonged torsion. Pregnancy test is also essential to rule out other causes of abdominal pain such as ectopic pregnancy [16]. Adnexal torsion must be distinguished from other cases of abdominal pain that span multiple organ systems including appendicitis, nephrolithiasis, gastroenteritis, pelvic inflammatory disease, gastroenteritis, and other ovarian masses [38, 46]. Ovarian

tumor markers specific to the pediatric and adolescent population which evaluate for germ cell tumors including lactate dehydrogenase (LDH), alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG), and cancer antigen 125 (CA-125) which evaluates for epithelial tumors should be obtained to evaluate for risk for malignancy in complex ovarian masses [47].

Although radiologic imaging can assist with diagnosis, adnexal torsion is a clinical diagnosis and imaging alone should not be used in isolation. Pelvic ultrasonography (US) with Doppler is the most commonly used imaging modality to evaluate for adnexal torsion. Transabdominal rather than transvaginal US is utilized in adolescents since many adolescents are not sexually active [25, 38, 48]. Findings on US which are concerning for adnexal torsion include unilateral ovarian enlargement or asymmetric enlargement of bilateral ovaries due to edema or adnexal mass, peripherally displaced follicles and heterogenous appearance of the ovary due to ovarian edema and ischemia, ovarian displacement toward the midline or contralateral side or uterine displacement away from the midline, which indicates tension due to torsion [8, 25, 38, 40, 41, 46, 49–51]. Ovarian volume ratio (volume of affected ovary divided by volume of unaffected ovary) greater than 20 has a high, positive predictive value for adnexal torsion [49]. Linam et al. found that adnexal volume less than 20 ml in menarchal females negatively predicted adnexal torsion in 100% of patients [52]. In menarchal females, the presence of an adnexal mass which exceeds 5 cm has a higher association with adnexal torsion. Conversely, pre-menarchal girls are more likely to have adnexal torsion in the absence of an adnexal mass [21, 38, 40, 46, 50].

Color Doppler evaluation can assist with diagnosis adnexal torsion by evaluating for presence of blood flow to the adnexa. Doppler should always be performed at the infundibular pelvic ligament (location of ovarian vessels) for accurate evaluation of arterial and venous adnexal flow. Although absent Doppler arterial flow and ovarian enlargement are classic findings in adnexal torsion, 45–61% of confirmed cases of adnexal torsion have normal Doppler findings with preservation of arterial flow [15, 46]. The sensitivity of absent arterial flow is as low as 40–73% with a recent meta-analysis showing sensitivity of 50% and moderate specificity at 87%. The whirlpool sign (twisting of the ovarian pedicle causing twisting of the vessels) is another pathognomonic Doppler finding for adnexal torsion [15, 38, 42, 46, 53]. Computed tomography (CT) and magnetic resonance imaging (MRI) are not recommended for initial evaluation for adnexal torsion, but may be beneficial to rule out other gastrointestinal pathologies or evaluate for anatomic anomalies [46].

Multiple studies have used retrospective data to create predictive algorithms to help triage patients with abdominal pain, streamline evaluation, and guide management of pediatric and adolescent adnexal torsion [15, 40, 52, 54–56]. Guided by their own retrospective data, Schwartz et al. performed the first prospective study using predictive composite scores for premenarchal and menarchal females with adnexal torsion. They found emesis, adnexal volume, and adnexal volume ratio were independent risk factors, for adnexal torsion could be reliably combined to create a composite score to better identify patients with torsion. Importantly, they found presence or absence of Doppler flow was not a good predictor of torsion, and

therefore was not included in the predictive scoring model. A score of 0–1 reliably excluded torsion, and a score of 4 or more predicted torsion in 25% of patients. The incidence of torsion in those patients with a score of 2–3 was 3–10% [56]. Future studies are needed to prospectively test and evaluate these scoring systems to increase generalizability of these predictive models.

Management and Outcomes

Adnexal torsion is a clinical diagnosis. Providers must evaluate the clinical history, physical examination, laboratory data, and imaging findings to determine the need to proceed with urgent surgery to prevent irreversible ovarian damage with the goal of adnexal conservation [47]. While some studies have shown an association of pain lasting longer than 10–72 hours with increased tissue necrosis, normal ovarian function has been reported 5 days after symptoms onset [44, 45]. Therefore, the duration of time of interrupted vascular flow needed to lead to irreversible damage of the ovary is unknown [2, 14].

The treatment paradigm for adnexal torsion has shifted from a more radical approach toward ovarian conservation surgery to preserve ovarian function [2, 14, 21, 27, 33, 43, 57–63]. In the past, oophorectomy was performed due to outdated concerns regarding the risk of malignancy in the affected ovary (low association between torsion and malignancy due to adhesions), increased thromboembolic events related to detorsion (no cases have been reported), continued pain due to adhesive disease, sepsis secondary to necrosis, and the thought that blue-black appearance of the adnexa was consistent with necrosis and non-functional ovaries [27, 44, 58, 64–67].

Multiple studies have demonstrated the inability of surgeons to reliably predict necrotic ovaries given viable ovarian tissue has been found in specimens deemed non-viable by visual examination [47, 49, 62]. In addition, the ovary has dual blood supply providing protection from ischemia, the blue-black color of the ovary may be due to venous congestion rather than ischemia, and multiple studies have shown ovarian function after detorsion of the adnexa [4, 14, 49, 54, 58]. Figures 28.1 and 28.2 demonstrate examples of adnexal torsion in patients with subsequent viable ovaries on follow-up imaging.

Abundant literature supports conservative management of adnexal torsion ideally with diagnostic laparoscopy, adnexal detorsion, ovarian or tubal cystectomy, and preservation of the adnexa including the ovary and fallopian tube even if necrotic [9, 14, 17, 58, 60, 62]. Ovarian and tubal cystectomy rather than cyst aspiration should be performed when possible to decrease the risk of cyst recurrence [9]. Some literature recommends initially untwisting the adnexa and repeating the US 6–8 weeks after initial surgery to determine if a cyst is still present and subsequent interval cystectomy is indicated [63, 65, 68]. Interval surgery may also be necessary in the setting of severely edematous and friable ovary that precludes the ability to perform a cystectomy without further damaging the adnexal structures [9]. Even

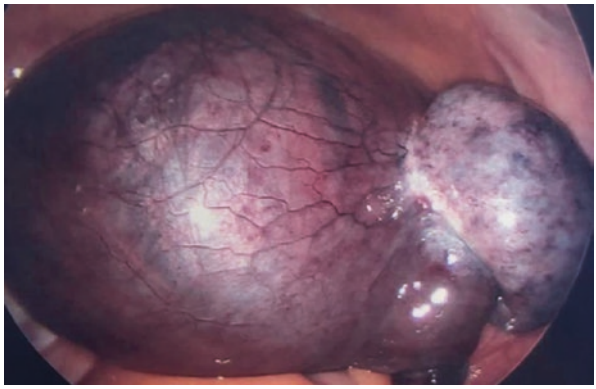

Fig. 28.1 Adnexal torsion due to a large paraovarian cyst. Right ovary and fallopian tube noted to be purple in color. A paraovarian cystectomy and ovarian preservation was performed. Post-operative ultrasound showed normal ovarian follicles indicating a viable ovary

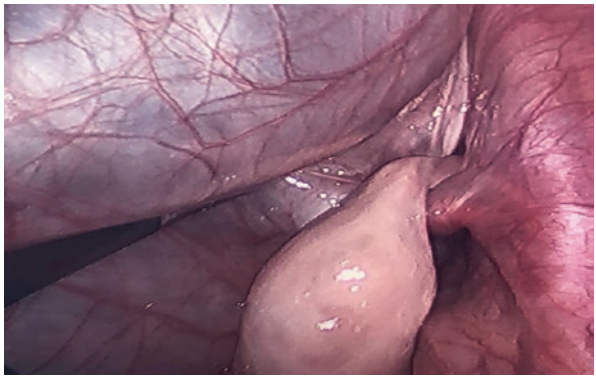

Fig. 28.2 Right adnexal torsion due to a large paratubal cyst with right ovary noted to be normal in color and size

with these recommendations, national data show that oophorectomy is still being performed far too often for adnexal torsion [27].

Limited guidance regarding the management of torsion in the setting of underlying endometriosis exists. Although conservative management with adnexal detorsion and cystectomy is recommended for most cases of adnexal torsion, the risks of concurrent tubal adhesive disease and obliteration of tubal patency must be considered in the setting of endometriosis. One case report utilized chromopertubation to assess tubal patency after adnexal detorsion. Documentation of contralateral tubal patency and the absence of free spillage from the affected fallopian tube led the authors to proceed with ipsilateral salpingectomy rather than cystectomy of the tubal endometrioma [32]. Until more data on the reliability of chromoperturbation in the setting of recent adnexal torsion is known, a conservative approach to management of adnexal torsion in the setting of endometriosis should include fertility-preserving surgery. Adnexal torsion secondary to endometriosis is rare and practice patterns should follow recommendations for management of general adnexal torsion.

Oophoropexy used to limit ovarian mobility and reduce recurrence of adnexal torsion remains controversial [69–73]. Oophoropexy should be considered in cases of recurrent torsion of the same adnexa, torsion of a solitary ovary after prior

contralateral oophorectomy, and potentially even in the setting of torsion of normal adnexa with elongated utero-ovarian ligaments [9, 51]. Recurrence rates of adnexal torsion have been reported to be 2–12% and even higher in cases of adnexal torsion in the absence of adnexal pathology [19, 49]. Multiple techniques for oophoropexy have been described including shortening the utero-ovarian ligament, fixation of the ovary to the peritoneum of the pelvic sidewall or utero-sacral ligament, or even suturing the ovary to the back of the uterus. Choice of technique depends on surgeon experience and pelvic anatomy [71, 72]. Even with oophoropexy, recurrence can still occur with a reported rate of approximately 9% in the pediatric and adolescent population [43, 74].

Controversy exists in the literature on the impact of oophorectomy and retention of torsed adnexa on future fertility. Certain studies suggest that oophorectomy can have a negative impact on fertility [75] while others state the opposite [76]. In the pediatric and adolescent population, multiple studies have shown the success of conservative management with ovarian retention for preservation of ovarian function, pubertal progression, and fertility in cases of adnexal torsion even when the ovary appears necrotic [4, 14, 17, 43, 47, 55, 58, 61–63, 77]. Furthermore, studies have shown normalized ovarian volume and follicular pattern on follow-up ultrasounds as high as 91–98% after initial detorsion after only 6 weeks [38, 55, 60, 62, 77, 78].

Surveillance US can be performed 6–12 weeks later to evaluate for cyst recurrence or persistence, ovarian viability, and need for interval cystectomy after the initial diagnosis of adnexal torsion. Some providers also consider performing long-term surveillance with annual US [9, 51]. Unfortunately, recurrence rates for endometriomas after initial surgery with cystectomy is estimated to be 6.4%, 10%, 19.9%, and 30.9% at 24, 36, 60, and 96 months, respectively, in one large study [79]. Hormone therapy, including combined estrogen/progesterone options (e.g., oral contraceptive pills, patch, and vaginal ring) or progesterone-only options (e.g., injectable depo medroxyprogesterone acetate or etonogestrel implant) can be used to suppress ovulation and therefore suppress future formation of functional cysts and hemorrhagic/corpus luteal cysts that can lead to adnexal torsion. These hormonal contraceptives do not prevent against non-functional cysts such as paratubal cysts, mature cystic teratomas, or cystadenomas because they are not formed from ovulation. Combined and progesterone-only hormonal therapies are also a mainstay of medical treatment for suppression of endometriosis [80, 81].

Conclusion

Adnexal torsion should be considered and radiologic evaluation of the pelvis should be obtained when pediatric and adolescent females present with acute abdominal pain associated with nausea and emesis. Evidence of an adnexal mass with or without Doppler flow abnormalities on ultrasound in the presence of concerning clinical presentation and physical exam findings should prompt consideration of surgical

confirmation of adnexal torsion. Although physiologic ovarian cysts are the most common instigator for adnexal torsion, endometriosis may increase the risk of torsion secondary to associated adnexal masses and adhesive disease leading tubal pathology. The recommended management of adnexal torsion is urgent diagnostic laparoscopy, adnexal detorsion, and ovarian preservation even when the ovary appears non-viable.

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Chapter 29
Ovary-Sparing Surgery for Ovarian Torsion in Adolescents

Joseph Nassif, Sally Khoury, and Marco Mouanness

Introduction

Definition and Prevalence

Ovarian torsion is the fifth most common gynecologic surgical emergency [1]. It is defined as the complete or partial rotation of an ovary or ovarian vascular pedicle about its long axis around the suspensory ligament of the ovary [2]. A 10-year review of 128 patients with adnexal torsion states that 2.7% of emergency gynecological surgery cases involved ovarian torsion [1].

Ovarian torsion can occur in infants, adolescents (pre and post-menarche) and adults. In the pediatric population, the peak incidence of ovarian torsion occurs during early adolescence and the immediate post-menarchal years [3]. Reproductive-age women have the highest prevalence of ovarian torsion, probably due to the increased occurrence of physiologic and pathologic ovarian masses, treatment for infertility, and occurrence of pregnancy. Torsion of the ovary and its pedicle both are uncommon occurrences in the pediatric and adolescent-age group with varying incidences depending on the institution, ranging from five in 100,000 girls aged 1–20 years to two in 10,000 patients [4], and constitute about 15% of all ovarian torsion cases with all ages included [1].

Torsion can involve the ovary and its pedicle alone, but more commonly involves both the ovary and fallopian tube (67% of cases of adnexal torsion). There are also cases of isolated torsion involving the fallopian tube alone (one in 1.5 million

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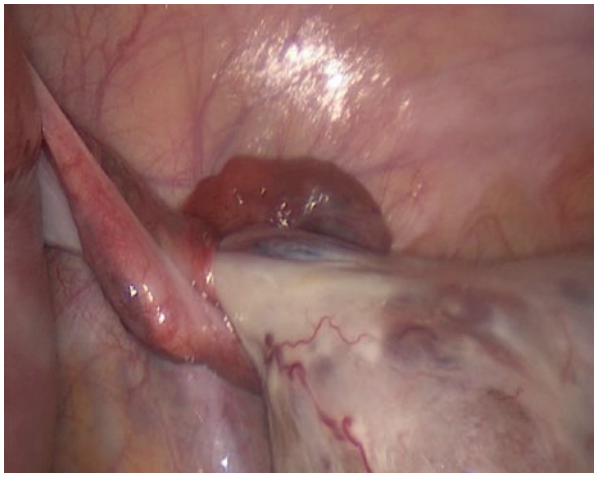

Fig. 29.1 Torsion of the right ovary in a 14-year-old patient

women) [3, 5]. Cases of torsion occur for many reasons, including the presence of an ovarian or Paraovarian lesion (Fig. 29.1).

Since it is a relatively rare cause of abdominal pain in this age group, accounting for up to 2.7% of all cases with acute abdominal pain in children [5], ovarian torsion in children is usually late to be diagnosed, and sometimes even missed. Unfortunately, despite its rarity, if ovarian torsion is not recognized and managed appropriately in a timely manner, it can result in loss of the reproductive potential of the corresponding adnexa. Definitive treatment to prevent gonadal necrosis is mainly time dependent, and emergent operative intervention remains necessary to allow for the survival of the gonad. Delays in diagnosis are also common because there is lack of specific symptoms, and due to the overlap of symptoms with more common pediatric conditions [6]. The clinical presentation of torsion of the ovary can masquerade as any acute intra-abdominal process (surgical or otherwise). In fact, when ovarian torsion is suspected, it is necessary to rule out other diagnoses like appendicitis, urinary stones or infection, mesenteric lymphadenopathy, pelvic inflammatory disease, ectopic pregnancy, etc. Therefore, one must approach all prepubertal girls with an acute abdomen with a high degree of suspicion for torsion of ovary, fallopian tube or both.

Overall, the rarity of the event, the lack of specific symptoms, and the likelihood of another diagnosis, all contribute to the delay in the diagnosis and management of an ovarian torsion in the pediatric and adolescent groups.

There has been a shift in current practice from oophorectomy to ovary-preserving surgery for cases of uncomplicated torsion in the pediatric population. Multiple studies have shown that ovarian-sparing approaches are a safe practice that allow ovarian salvage in the majority of pediatric patients even despite ischemic appearing ovaries. Laparoscopy is the preferred strategy for diagnosis and management of ovarian torsion.

Predisposing Conditions and Protective Factors

Different predisposing conditions exist depending on the age of onset of torsion.

Torsion of a normal-appearing ovary is an unusual event, but is mainly present in the adolescent population. In fact, in adolescent and premenarchal populations, 50% of the ovarian torsions occur on normal-appearing ovaries [7].

Some of the postulated causes for torsion of a normal adnexa include the following [8–10]:

- Hypermobility of the fallopian tubes or mesosalpinx
- Laxity or elongation of the pelvic ligaments (mainly the infundibulopelvic ligament)
- Fallopian tube spasm
- Strenuous exercise
- Abrupt changes in intra-abdominal pressure
- Increased hormonal activity in the premenarchal period or even in the perinatal period [8]

The presence of any mass on the ovary might predispose it to rotation along its axis. These masses include but are not limited to large heavy cysts and cystic neoplasms, such as teratomas, hemorrhagic cysts, cystadenomas and endometriomas. Note that it is rare to see ovarian torsion from cysts that are smaller than 5 cm [7, 11].

It is also worthy to note that studies have shown that right ovary is more likely to twist than the left ovary, with a ratio of 3:2 [3, 12], in the presence or absence of predisposing factors. This is probably due to the more stable suspension of the ovary on the left side because of the sigmoid colon that occupies the majority of the space [6, 12], or a less stable ovary on the right side due to the hypermobile cecum.

In the post-menopausal adolescent period, gestation can be a risk factor for ovarian torsion due to the increased rate of ovarian masses during pregnancy. Reasons for large cysts in pregnancy may include hyperstimulation syndrome, theca-lutein cyst of pregnancy, and molar pregnancy.

Some conditions, by their inherent capacity to increase intra-abdominal adhesions, may infer a protective value against torsion by rendering the ovary immobile. These conditions include pelvic inflammatory disease, endometriosis, adhesions, intra-abdominal infections, and malignant neoplasms [12, 13]. Endometriomas, however, unlike endometriosis, increase the risk of ovarian torsion and are therefore recommended to be removed if they are larger than 3 cm [14].

Ovarian torsion is more likely to occur with a benign tumor than in a malignancy. In fact, a study of reported case series has shown that the incidence of ovarian torsion with ovarian malignancy was <2% [15].

Anatomy and Pathogenesis

There are two main ligaments that attach to the ovary and allow suspension of this organ in the pelvis:

- Infundibulopelvic ligament (also called suspensory ligament of the ovary) suspends the movable ovary and attaches it to the pelvic sidewalls. It allows the ovary to position either laterally or posteriorly to the uterus. The ovarian vessels travel along the infundibulopelvic ligament and allow proper vascularization of the ovary.
- Ovarian ligament (also called utero-ovarian ligament or proper ovarian ligament) is composed of muscular and fibrous tissue, and attaches the ovary to the uterus directly below the insertion of the fallopian tubes. It lies within the broad ligament and contains blood supply to the ovary from the uterine artery.

Since the adnexa are not fixed structures, any big leading point such as a mass or a cyst can lead to the rotation of the infundibulopelvic ligament or the ovarian ligament along their own axis, thereby inducing twisting and ovarian torsion.

Diagnosis

Symptoms and signs of an ovarian torsion are directly related to its pathophysiology. Initially, the rotation of the ovary will cause a twisting of the suspensory ligament and the vasculature pedicle that runs through it. Because arteries have thick, muscular walls and are less collapsible than veins, the initial consequence is a compromise of the venous and lymphatic flow resulting in diffuse ovarian edema and enlargement. Over time, this edema will cause a distension of the ovarian capsule and an increase in intra-uterine pressure which will lead to compromise of the arterial flow with arterial thrombosis. Ultimately, this will lead to ischemia and infarction of the affected ovary, and if left untreated can cause systemic infection and inflammation.

Note that with incomplete torsion (or torsion/detorsion syndrome), the arterial inflow is not compromised, and capillary hydrostatic pressure remains increased thereby obstructing lymphatic and venous drainage which will result in massive ovarian edema.

The non-specificity of the symptoms and the long list of differential diagnoses make the diagnosis of ovarian torsion quite difficult. This is still the case with experienced hands and availability of multi-modal imaging techniques. Nevertheless, the timely and correct diagnosis of ovarian torsion has a vital role in the protection of the ovaries (for preservation fertility and hormonal status of the patient). A delayed diagnosis of ovarian torsion (pain >10 hours) [16] may cause severe morbidity, including, but not limited to, ovarian necrosis, peritonitis, and sepsis [6, 7].

Clinical

Adolescent and pediatric torsions differ from adult torsion by multiple criteria. Adult torsion of the ovary is usually associated with an ovarian mass (benign or malignant) causing axial rotation of the ovary along its suspensory ligament. Unlike adult torsion, adolescent and pediatric ovarian torsions are most commonly caused by a physiologic cyst (including in-utero) or a benign adnexal mass. It is therefore important in these cases to act quickly in order to preserve normal ovarian tissue.

The clinical presentation in ovarian torsion can be quite variable. Typically, pain is present in almost all cases of torsion. This pain is usually sudden, severe, intermittent, localized in one of the lower quadrants, and associated with peritoneal signs and a palpable adnexal mass. However, it could also be dull and chronic pain in nature with frequent bouts of exacerbation. Exacerbating factors include sexual intercourse, defecation (or any bowel movement), urination, and mobilization.

A patient could also present with nausea and vomiting, pyrexia associated with leukocytosis, or a palpable adnexal mass on examination [13–15]. It is important to note that any patient of reproductive age presenting with abdominal pain should undergo a urine pregnancy test to rule out a pregnancy.

The presence of peritoneal signs or "surgical abdomen" should prompt the physician to think about torsion as the underlying cause and pursue emergency surgery.

Imaging

Multiple modalities can help with the diagnosis of ovarian torsion, especially when the patient's presentation is not straightforward. Some modalities might be ordered for the purpose of eliminating other diagnoses (genitourinary, gastrointestinal, or other gynecological causes), and others might be performed to aid in the diagnosis and management of ovarian torsion.

Gray-Scale Ultrasound

Ultrasound should be considered as the primary modality to evaluate a young female patient who presents with lower abdominal pain and suspected to have ovarian torsion because it is noninvasive, accessible, and cost effective. In fact, when the clinical diagnosis is not clear based on symptomatology and signs, the first imaging modality that should be used is ultrasonography. The sensitivity and specificity of this modality are not very high, with reported detection rates ranging between 46% and 74%. One series studying the effectiveness of US in diagnosing ovarian torsion yielded a positive predictive value of 87.5% and specificity of 93.3%, corroborating

the potential for expeditiously making this diagnosis when the findings are clear on ultrasound.

Findings on gray-scale ultrasound, which can be visualized at any age, include [17] the following:

- Enlargement of the ovary: enlargement of the ovary, with or without the presence of an ovarian mass, remains the most common finding associated with torsion on gray-scale ultrasonography [3]. This enlargement can be seen early on in the process of the disease even before infarction has occurred. Ovarian enlargement is defined as a maximal diameter greater than 4 cm or as a volume greater than 20 cm^3 in a pre-menopausal woman and greater than 10 cm^3 in a premenarchal or post-menopausal woman. Some studies have shown that the twisted ovary averages 28 times the normal size, and that the surrounding stroma can be heterogeneous due to the accompanying edema and hemorrhage [18]. An easier method for checking ovarian enlargement is comparing the size of the suspected torsed ovary to the contralateral ovary [3]. However, the size of the ovary is normal in 5% of cases of torsion. Therefore, a normal-sized ovary does not rule out the diagnosis of ovarian torsion on ultrasound [2].
- Displacement of the ovary.
- Presence of an ovarian mass.
- Presence of free fluid in the cul de sac (Douglas' Pouch).
- Peripheralization of ovarian follicles: A specific finding of ovarian torsion in adolescents is the presence of multiple small follicles at the periphery of an enlarged ovary [3].
- Thickening of a cyst wall.
- Twisted pedicle.

In 74% of cases, we can see a combination of a unilaterally enlarged ovary with multiple uniform small peripheral follicles and an afollicular central stroma [17, 18].

Spectral Doppler Ultrasound

Spectral Doppler ultrasound has been studied as an adjunctive modality in the diagnosis of ovarian torsion. The aim of this modality is to study the vasculature flow pattern of the ovarian vessels in order to diagnose an ovarian torsion and determine the extent of compression/injury. In fact, the flow pattern depends on the degree of vascular obstruction and the chronicity of the torsion, which first affects the venous and then the arterial blood flow [19].

Due to the pathophysiology of the disease, there is wide discrepancy reported in the literature concerning the use of spectral Doppler ultrasonography for ovarian torsion. In patients who were diagnosed to have ovarian torsion by pathology, abnormal Doppler flows were reported in variable percentage, ranging from 35 to 93% in some case series [20, 21].

Due to the qualitative nature of the assessment of the flow patterns on ultrasound (normal, decreased, or absent), it is relatively difficult to generalize the results of one or more study. Evidently, the ultrasound features are subject to different interpretations depending on the operator.

It is important to note as well that the presence of arterial flow on spectral Doppler ultrasound does not rule out the diagnosis of ovarian torsion. In fact, the ovary receives a double supply of blood: one from its own artery (the ovarian artery) and one from arterial branches of the uterine arteries. Moreover, the effect of the torsion on the flow pattern depends largely on the level of vasculature compression and chronicity of the torsion. Therefore, the studies of the arterial or venous flow of the ovarian vessels on spectral Doppler ultrasonography may not rule out the diagnosis of ovarian torsion.

In fact, the most common finding in a series of ovarian torsion studies was either the decrease or the absence of venous flow (93%) [20, 21], probably due to early collapse of the compliant venous walls. The dual blood supply of the ovary and the edema resulting from the venous thrombosis itself might explain why in some cases of ovarian torsion we have persistence of arterial waveform on spectral Doppler ultrasound.

Color Doppler might help in the diagnosis of ovarian torsion when a "whirlpool sign" is clearly visible. "Whirlpool sign" is the characteristic swirling target appearance of the ovarian vessels along the axis of the pedicle. It has been reported in varying percentages, ranging from 13 to 88% in ovarian torsion. The presence of this sign along with an enlarged ovary is diagnostic of ovarian torsion [17].

MRI/CT

Adolescents with non-specific acute abdominal pain may undergo other imaging modalities (CT or MRI) as first-line imaging to rule out differential diagnoses.

Moreover, the utility of MRI as an adjunctive imaging has been proven in cases where ultrasound and clinical symptoms are inconclusive for the diagnosis of ovarian torsion. In fact, MRI has the advantage of identifying early changes to the ovarian stroma and its surrounding tissue, mainly due to edema and hemorrhagic infarction [22].

X-Ray

Plain abdominal X-rays are less effective in detecting ovarian torsion but might be used a conjunctive tool to rule out other causes of acute abdominal pain in this population, including bowel obstruction and renal calculus.

Laboratory Tests

The diagnosis of ovarian torsion remains mainly a clinical diagnosis supported by ultrasonographic evidence. However, basic laboratory investigations need to be performed to rule out differential diagnoses in acute abdominal pain in a reproductive-age woman, including urine pregnancy test, urine analysis, and complete blood count.

In the case of an incidental finding of a suspicious ovarian tumor as the cause of the torsion, serum levels of tumor markers should be investigated. They include alpha-fetoprotein (αFP), beta-human chorionic gonadotropin (β-HCG), lactate dehydrogenase (LDH), carbohydrate antigen (CA) 125, and CA19–9 [8, 23].

Management

A retrospective study showed that misdiagnosis was more likely to be made in premenarchal girls than in menstruating women [24].

Torsion initially compromises the low-pressure venous and lymphatic outflow, leading to ovarian edema and enlargement. Over time, arterial circulation is compromised, resulting in thrombosis, ischemia, and hemorrhagic infarction.

Detorsion was initially described in 1946 by Way as a safe and effective treatment for ovarian torsion. At that time, and for decades onward, ovary-sparing surgery for ovarian torsion was not the preferred option [25].

Surgeons were even more reluctant to do ovary-sparing surgery if the ovary was ischemic in appearance because of the possibility of morbid complications such as thromboembolism, malignancy, or even peritonitis. However, recent data have shown that the rate of these complications is relatively low, allowing ovary-sparing surgery to be used as a safe and efficacious alternative treatment for ovarian torsion. Moreover, long-term follow-up has shown that the ovaries continue to function despite an ischemic appearance during the salvage surgery [26–28].

Recent studies have demonstrated variation in practice patterns between general surgeons and gynecologists, with gynecologists more likely to perform ovarian preservation for torsion than general surgeons (94% vs 6%) [29, 30]. Trotman et al. showed in a recent study that the addition of a pediatric and adolescent gynecologist to the hospital team leads to a decrease in the rate of oophorectomy for benign diseases and a beneficial effect on the rate of ovarian-conserving procedures compared to pediatric surgeons [31]. A collaboration between the pediatric surgeons and the gynecologists has also been shown to be beneficial in decreasing the rate of unwarranted oophorectomy in the adolescent group [31].

Surgical

Surgical treatment options for ovarian torsion include mainly detorsion alone, detorsion with oophoropexy, and oophorectomy. We will discuss the advantages of opting for laparoscopy instead of laparotomy, and for ovary-sparing surgery (detorsion with or without cystectomy) instead of oophorectomy.

Laparotomy Versus Laparoscopy

Once the diagnosis of ovarian torsion is made, prompt surgical intervention is required. In the past, the standard treatment for ovarian torsion was laparotomy. However, over the years, a switch to a less invasive laparoscopic approach was made. In fact, laparoscopy has similar outcomes compared with laparotomy, with less morbidity and quicker recovery time [32], and it has been shown to be safe in young girls [33–35].

Laparoscopy remains currently the most reliable diagnostic and therapeutic approach. A retrospective study conducted by Cohen et al. [36] showed similar outcomes between laparotomy and laparoscopy when it comes to post-operative ovarian function, with shorter hospital stay and less hospital stay in the arm undergoing laparoscopy. Thus, laparoscopy can be used as a safe diagnostic and therapeutic tool.

Oophorectomy Versus Ovarian Sparing Detorsion

The traditional treatment for ovarian torsion was the removal of the adnexa of the corresponding side (oophorectomy). It was thought that detorting the ovary and leaving it behind might lead to several complications, including but not limited to thromboembolic events due to the detorsion, systemic inflammatory reaction, and sepsis due to the presence of a non-viable organ, and potential malignancies due to the remaining tissue [37, 38] (Figs. 29.2, 29.3, and 29.4).

However, recent data have shown that "detorsion," a more conservative approach, is a safe and better alternative to oophorectomy allowing mainly ovarian preservation [26–28, 39, 40]. In fact, studies have shown increased reproductive morbidity among adolescents who receive a unilateral salpingo-oophorectomy because they have up to a 15% lifetime risk of torsion or neoplasia of the contralateral ovary, a reduced ovarian reserve, and are more commonly referred for infertility evaluation [31].

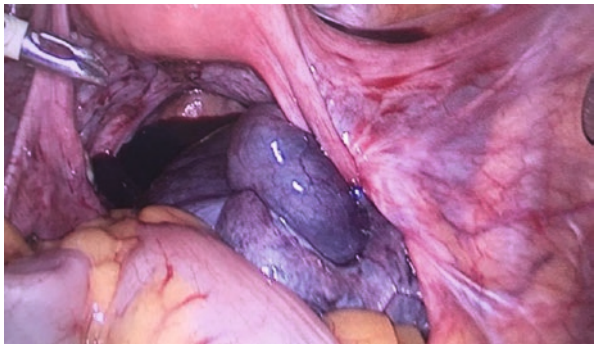

Fig. 29.2 Ischemic torsion of the right ovary in a 16-year-old patient

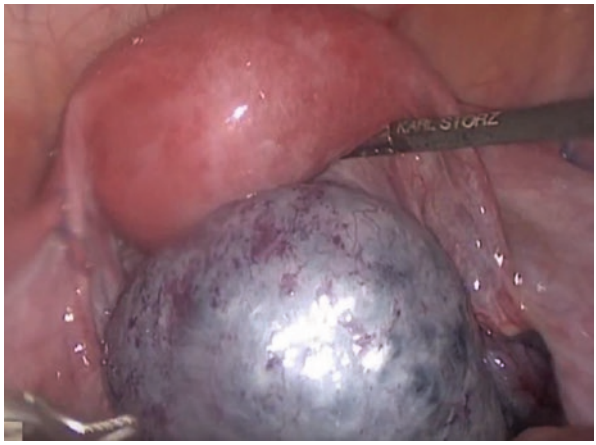

Fig. 29.3 Enlarged torsion of the right ovary with a complex cyst of 7 cm in a 13-year-old patient

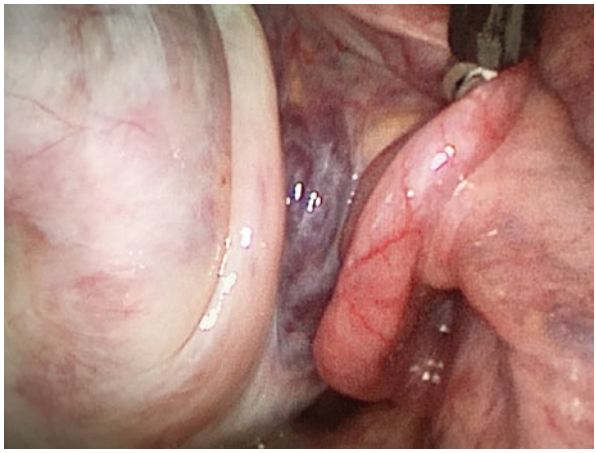

Fig. 29.4 Torsion of the infundibulopelvic and utero-ovarian ligaments in a 14-year-old patient

Risk of Thromboembolic Events

The risk of pulmonary embolism is often quoted as the primary indication for oophorectomy instead of detorsion. The event is thought to be due to the potential release of a thrombus from the detorted vascular pedicle. However, no case of a thromboembolic event following ovarian detorsion has ever been reported in the literature. The reported rate of pulmonary embolism in cases of ovarian torsion is only 0.2%, and studies have shown that detorsion does not increase that incidence [41].

A study done by McGovern et al. showed two cases of pulmonary embolism both of which were in the group that underwent oophorectomy [42].

Risk of Malignancy

Only 1% of all malignancies in childhood are ovarian [11]. Ovarian torsion has been associated with an underlying malignancy in only 1.8% of cases [43, 44]. In fact, most studies on twisted ovaries showed no underlying histopathologically malignant disease.

Most of the cases of malignancy-associated ovarian torsion are found to be at an early stage. In fact, advanced intra-abdominal malignancies are associated with severe inflammation and adhesions, thereby making it a protective factor against ovarian torsion. Nevertheless, correct intra-operative clinical judgment should orient the attending surgeon toward the proper management. A torsed bluish-black ovary might make the diagnostic orientation more difficult [45]. In these cases, or in cases of high suspicion of malignancy, an intra-operative frozen section might be needed to identify the histopathological type of tumor.

Factors that increase the suspicion of malignancy in tumors associated with ovarian torsion in adolescents and children include the following: precocious puberty, mass larger than 8 cm in size with a solid area, and elevated tumor markers (β-HCG, αFP, LDH, and CA125). However, elevated levels of serum tumor markers can be associated with benign tumors, and a low level of serum tumor markers does not exclude malignancies. A low level of tumor markers is not an absolute indicator to exclude presence of malignancies. Therefore, preoperative risk stratification should without a doubt assist surgeons in their decision-making for preserving the ovaries.

However, there is no evidence to support a benefit of oophorectomy over detorsion owing to the concern for missing an occult malignancy. The risk of malignancy should not be used to justify oophorectomy given the low incidence of malignancy. Those ovaries with a malignant lesion are frequently evident during the operation. If there is concern, an intraoperative frozen section can also be considered. Only if there is clear clinical evidence of a malignancy should an oophorectomy be considered.

Fertility Preservation

Second look surgeries (after primary surgery for ovarian detorsion) have documented normal appearance of detorted ovaries. This was also true in cases where the ovaries appeared to be ischemic before detorsion on the initial diagnostic/therapeutic surgeries [46, 47].

Studies on the outcomes of detorsed ovaries have reported the presence of follicles in more than 88% of cases on ultrasound [41, 48–51].

Long-term follow-up of ovarian detorsion cases have allowed people to further study the rate of future pregnancies. Successful pregnancies and live births have been noted following ovarian detorsion and ovarian preservation in adults. Oocytes were also successfully retrieved from detorted ovaries suggesting that the remaining ovary is still functioning. Only 5% of the patients with subfertility problems related to torsion, required in vitro fertilization [46].

A shift of ovarian preservation in children and adolescents presenting with ovarian torsion reflects the increasing concern for maintaining fertility during subsequent childbearing years. The clinical appearance of the ovary at the time of detorsion may not be the best indicator of parenchymal viability; therefore, ovarian preservation despite the outward appearance of the gonad should be the operative priority [29, 52–54].

Ovarian Appearance at Time of Surgery

In early stages of torsion, venous drainage is impaired, resulting in engorgement and characteristic blue-black appearance of the ovary. It is important to note that arterial perfusion can be maintained for several days following torsion [55]. Therefore, ovaries that have undergone torsion are often engorged and appear necrotic at the time of primary surgery, and this appearance is unlikely to change immediately after detorsion. Clinicians are often inclined to remove the affected ovary simply because of their appearance at the time of the surgery [56]. Many studies have demonstrated the presence of follicles on post-op ultrasound of patients who had severely enlarged and “necrotic-like” ovaries at the time of surgery [53, 57, 58]. Moreover, the affected ovary was undistinguishable from the unaffected ovary on follow-up ultrasound [58]. Other studies demonstrated the presence of viable ovarian tissue on pathology of an oophorectomy specimen sent for ovarian necrosis due to torsion. Therefore, the gross appearance of the ovary at the time of diagnostic/therapeutic surgery for torsion does not correlate well with ovarian viability and should not be used as a sole determinant of ovarian resection.

Follow-Up

A follow-up ultrasound, most commonly performed at 3 months post-op, should be considered after a detorsion procedure to document the presence of ovarian follicles. It is wise to consider earlier imaging if there is concern for malignancy/neoplasm.

Strict abdominal pain warnings should be given, as there is always the risk of recurrence of the torsion on the ipsilateral or contralateral ovary.

Cystectomy and Bivalving

A study [50] also advocated additional procedures during detorsion, which include cystectomy, aspiration, and bivalving. However, only detorsion is recommended to be performed in the "blue-black" ovaries. Cystectomy should be carried out probably 6 weeks later if the cyst persists. Technically, it would be more difficult to enucleate the cyst from the gangrenous ovarian tissue and secure the hemostasis. Styer and Laufer suggested bivalving for the detorted ovaries to reduce the ovarian intracapsular pressure while increasing arterial perfusion. They reported normal follicular function in 4 of the 5 patients who underwent bivalving [50].

Oophoropexy

Oophoropexy is a surgical procedure in which one ovary or both ovaries undergo fixation, a procedure in which the ovary is elevated and fixed to a non-mobile structure to reduce the risk of retorsion. It is the most common procedure for prevention of ovarian torsion recurrence. In fact, patients with a history of ovarian torsion, especially if torsion happened on a normal adnexa (no masses), have a high risk of recurrence of torsion on the ipsilateral or contralateral ovary [59, 60]. Reports by several authors indicate a recurrent torsion risk in pediatric population ranging from 5% and 18% [61, 62].

Several techniques of oophoropexy have been reported, without any unified consensus on the best approach [63–65]. The techniques include either suturing the ovary to a fixed structure or reducing the length of the ovarian ligaments by plication. Permanent non-resorbable sutures are recommended for all of these procedures, but surgical clips have also been advocated as a good alternative for fixation to the sidewall. The ovaries can be sutured to multiple structures depending on feasibility: pelvic sidewall (usually at the level of the pelvic brim) [63–65], uterosacral ligaments, or posterior myometrium.

In cases of torsion of the ovary in normal-looking adnexa, where an elongated utero-ovarian ligament is identified, plication of the utero-ovarian ligaments can be used to reduce the risk of recurrence. The techniques used to perform the plication include either suturing the proximal end of the ligament to its distal end [66], or shortening the ligaments by placement of an endoloop [67].

It is important to identify the ureters and the iliac vessels before performing these surgeries to avoid any injury. Plication of the utero-ovarian ligament is the preferred technique for oophoropexy since it has less effect on future fertility and is easy to perform laparoscopically [68–70].

Oophoropexy is not a complication-free procedure. Due to the interference with the fallopian tube blood supply, decreased tubal function, and decreased communication between the ovary and the tube, oophoropexy has been shown to reduce future fertility [70]. Furthermore, endoloop placement is associated with tissue necrosis at the site of insertion [69].

Although oophoropexy is not without complications, it remains preferable in certain situations such as recurrent torsion, the presence of a single ovary, bilateral torsion, or torsion of a normal-appearing ovary. It is worthy of note that despite oophoropexy, the risk of recurrence is not completely eliminated [71].

Prognosis Without Treatment

If left untreated, ovarian torsion can lead to severe local and systemic complications. Local complications include necrosis of the ovary, loss of fertility and hormonal status, and peritonitis requiring emergent surgery. Systemic complications include SIRS (systemic inflammatory response syndrome), sepsis, and multiple-organ failure. Fatal complications following ovarian torsion have also been reported. Fitzhugh et al. [72] reported a case of a four-month-old infant with ovarian torsion and bowel necrosis that led to cardiorespiratory arrest and eventually to the death of the infant. Havlik et al. [73] also reported a case of sudden death from ovarian torsion and suggested that adnexal torsion should be included as a differential diagnosis in cases of sudden death in infancy.

Conclusion

Ovarian torsion should be suspected in adolescent girls with abdominal pain. The diagnosis remains a great challenge because of the non-specific manifestations and lack of specific diagnostic tools. Laparoscopic detorsion is the treatment of choice regardless of the color of the ovaries during the surgery. Oophoropexy should also be individualized in patients with ovarian torsion.

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Chapter 30
Adnexal Torsion in Adolescent and Pediatric Patients

Oshri Barel and Moty Pansky

Introduction

Adnexal torsion in patients under 18 years old is quite rare; most cases of ovarian torsion occur in reproductive-aged women between 20 and 40 years old [1]. However, among pediatric patients, the incidence of adnexal torsion is about 5/100,000 cases [2]. Most cases occur in patients with ovarian cysts or fallopian tube cysts that act as an extra weight that makes the adnexa more susceptible for rotation and eventually twists the adnexa; nevertheless, some cases involve torsion of a normal ovary. Adnexal torsion in adolescent and pediatric patients is diagnosed and treated mostly either by gynecologists or pediatric surgeons. The timing of intervention is important in order to preserve the twisted ovary and avoid future fertility impairment.

Epidemiology

Diagnosis

The diagnosis of adnexal torsion is always difficult, even more so in adolescent and pediatric patients [3]. In about 50% of adult patients with presumed torsion, this diagnosis is eventually ruled out in laparoscopy. No imaging or laboratory test is 100% sensitive and specific, so the only means of reaching a definitive diagnosis is surgery. Pediatric and adolescent patients sometimes find it hard to report all of their symptoms, and gynecological examination is usually limited in this population, making the diagnosis even harder. Many clinical factors have been reported in

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association with adnexal torsion, these include acute onset of pain that is usually intermittent in nature accompanied by nausea and vomiting. On imaging, the ovary often looks edematous and larger than the other ovary, with enlarged follicles. Blood flow to the ovary may be decreased or absent and a typical whirlpool sign may be present on Doppler ultrasound imaging [4, 5]. Also, the levels of IL6 might be increased but this is not usually taken as a routine laboratory test.

Beth et al. [6] have formulated a composite score in order to better predict the possibility of adnexal torsion in pediatric and adolescent patients. This score combines adnexal volume of over 6 ml, the presence of vomiting and an adnexal ratio between the affected and non-affected ovary of more than 1.25 to create a composite score in order to better predict the possibility of ovarian torsion. Doppler blood flow to the ovary was not found to be a reliable predictor of ovarian torsion in their study. Melcer et al. [7] reviewed 87 cases of torsion in patients under 18 years old, and found a 60% accuracy in preoperative diagnosis. The rate of accurate diagnosis was actually higher in premenarchal girls (100%) compared with postmenarchal girls (48.5%). They also found that nausea and vomiting were predictive of ovarian torsion, another predictive factor were clinical signs suggestive of peritoneal irritation; however, on multivariate analysis, only ultrasound findings of enlarged ovaries and younger patients' age were found as significant predictors of ovarian torsion. Patients with adnexal torsion were more prone to have leukocytosis on blood count, enlarged ovaries on ultrasound scans, and free pelvic fluid. Another study by Melcer et al. [3] compared adult cases of torsion with cases in patients less than 18 YO and found that torsion of adnexa with para-ovarian cysts was more common in the adolescent and pediatric population. The likelihood of recurrent torsion in their study was similar between adult and pediatric patients. Another study by our group [8] found that torsion on hydatids of Morgagni was found in 26% of adolescents undergoing laparoscopy for ovarian torsion in their institute. In some cases, the torsion involved the entire adnexa while in others only the cyst was involved. This was significantly higher than in the adult population.

The most common diagnosis in teen postmenarchal patients undergoing laparoscopy for presumed torsion and eventually do not have adnexal torsion is usually a functional ovarian cyst – mostly hemorrhagic corpus luteum cyst [7].

The diagnosis of adnexal torsion remains a difficult clinical diagnosis and a high index of suspicion is required in order to be able to preserve the affected adnexa, this should be weighed against the possible risks of surgery.

Treatment

The main form of treatment in patients less than 18 years of age involves detorsion of the adnexa in order to preserve ovarian function and to avoid an impairment of future fertility. Although some cases of adnexal torsion resolve spontaneously, a

delay in diagnosis might result in loss of function of the involved adnexa. However, a survey of pediatric patients with torsion performed by the National Inpatient Sample in 2015 revealed that more than 60% of pediatric patients in the United States underwent oophorectomy due to this condition [2].

Many possible reasons can motivate surgeons to remove a twisted ovary: some believe that the necrotic appearing ovary might not be viable in the future, some fear underlying malignancy, and some fear that leaving a necrotic looking ovary in the abdomen might increase the risk of abdominal adhesion and chronic pelvic pain. However, most ovaries resume normal function following detorsion [9–11].

Different studies have dealt with the possible risk of leaving a malignant tumor behind when performing an adnexal detorsion for a pediatric patient, especially when dealing with enlarged and cystic ovaries. The incidence of malignancy in adults with adnexal torsion is around 2% [12]; this incidence is probably lower in younger patients. In two case series [13, 14], including 126 cases of ovarian torsion, no cases of malignancy were diagnosed. Guthrie et al. evaluated 1232 pediatric patients with ovarian torsion [2] and found that the incidence of malignancy was 0.4%. Others have found a higher incidence of 1–5% [15, 16]; however, most cases of ovarian malignancy were clear prior to or during the time of surgery. Tumor markers such as alpha-fetoprotein or CA125 can be helpful but are usually less practical in this condition due to the time it might take to return from the laboratory. A higher likelihood of malignancy exists if the ovarian cyst is larger than 8 cm [17]. Dasgupta et al. [18] concluded that there is no evidence to support oophorectomy over detorsion due to this reason unless there is a clear clinical evidence of ovarian malignancy during the operation or after the initial workup.

An ovarian cyst can be difficult to treat while the ovary is still edematous and engorged and may lead to an unplanned oophorectomy; therefore, we recommend evaluating if this is feasible during surgery and then decide whether to proceed with a cystectomy or to detort the ovary and plan a second laparoscopy and cystectomy. If malignancy is confirmed by biopsy then oophorectomy and further treatment will be required; however, we recommend not to act radically only upon the findings in the frozen section but to await the final histopathology report. This will allow for more accurate diagnosis and time to discuss treatment options with the patient and her family and to plan the next procedure.

Some have also raised the possibility of pulmonary emboli dislodging from the twisted ovarian vein and migrating into the lungs following detorsion, no such case was ever reported in the literature [18]; however, two cases of PE were reported following salpingo-oophorectomy for adnexal torsion [19].

A number of studies [20, 21] have looked at pharmacological treatment in order to protect the ovary from an ischemia-reperfusion injury that might ensue following ovarian detorsion. Free radicals from the ischemic tissue might be released and further damage the untwisted ovary. Animal studies are still looking at the role of anti-inflammatory and antioxidant drugs for this purpose.

Torsion of the Fallopian Tube

Isolated fallopian tube torsion is a rare entity in adults, with an incidence of 1:500,000 in adults and is reported to be even rarer in children and adolescents [22]. Risk factors for fallopian tube torsion include fallopian tube cysts (mostly hydatids of Morgagni) or para-ovarian cysts, hydrosalpinx and hematosalpinx – these may arise following previous surgery or pelvic inflammatory disease. Patients usually present with pain and nausea or vomiting, the pain is usually localized and hard to control with analgesia. The diagnosis of isolated tubal torsion is often delayed by more than 48 hours due to the difficulty in diagnosis. This condition is hard to diagnose due to the fact that imaging of the fallopian tube is difficult, especially if no tubal cysts are present, while the ovaries appear normal in ultrasound. A delay in diagnosis might cause necrosis of the tube, and sometimes following tubal detorsion, hydrosalpinx may ensue. The difficulty in diagnosis might explain the reported rarity of this condition.

In cases of hydrosalpinx that caused tubal torsion, performing neosalpingostomy in premenarchal girls can preserve the fallopian tube [23].

Prognosis

Upon looking at a twisted adnexa in surgery, it often looks enlarged, engorged, edematous, and the color of the ovary and tube is often blue, purple, or black. The reason for that is the fact that often, the ovarian vein is the first to occlude following the torsion; this causes edema and discoloration of the adnexa; only later, in most cases, the ovarian arterial blood flow is impaired. The question arises whether to perform an oophorectomy or to preserve the ovary.

It has been shown that even a grossly ischemic and necrotic appearing ovary resumes its normal function in the following months after detorsion [24, 25]. Postoperative imaging usually demonstrates resumption of ovulation and follicle formation [24] in these ovaries, and pregnancies have been reported in patients with twisted single ovaries [25]. Santos et al. [11] evaluated 29 cases of ovarian torsion in pediatric and adolescent patients, all patients underwent detorsion, some with oophoropexy. More than 96% of patients resumed normal ovulation and function of the affected ovary in long-term follow-up. Zhai et al. [26] found that women who underwent detorsion of the adnexa as children had more menstrual irregularity and dysmenorrhea than patients that have undergone oophorectomy.

Some authors have suggested performing a frozen section of the ovary in order to determine if necrosis is present and then deciding whether to remove the ovary or preserve it [27]. We believe that the bulk of the current literature supports ovarian preservation even if it appears necrotic and does not necessitate a frozen section.

Prevention

Recurrent ovarian torsion can occur in 5–18% of pediatric and adolescent patients [3, 13]; predisposing factors include long fallopian tubes, long and lax utero-ovarian ligaments, patients with torsion of normal ovaries and premenarchal patients with torsion [28–30]. Oophoropexy is not indicated in cases of first torsion but should be considered in cases of recurrence. Oophoropexy can be performed by either fixating the ovaries to the anterior abdominal wall using non-absorbable sutures or by shortening the utero-ovarian ligament using a plicating suture. Possible risks of oophoropexy include damage to the adnexal blood supply, impairment of fertility due to the change in anatomical position of the tubes and ovaries and the possibility of a recurrent torsion despite the procedure [14, 31, 32].

Follow-Up

In pediatric and adolescent patients, we recommend that a follow-up ultrasound should be performed following detorsion to demonstrate the generation of new follicles in the involved ovary and to exclude possible hydrosalpinx. This should probably be done 3–6 months following the initial procedure due to the fact that resumption of normal blood supply and function of the ovary might take up to 2–6 months [33] following detorsion in postmenarchal patients.

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Chapter 31
Adolescent Endometriosis

Jhemma Zeilger and Ceana H. Nezhat

This is my story. And I emphasize "story" because I have come to the deep realization over many years of determined effort and disciplined self-introspection that our life is the story we choose. We create it. We write it. Most importantly, we have the power to rewrite it in every moment.

I should like to explain from the start that the diagnosis and label of "endometriosis" at the tender age of 11, which at the time felt like a long, slow, death sentence, ultimately proved to be an incredible blessing. I'd witnessed my mother plagued with the disease since I could remember. It was my understanding that endometriosis never fully "goes away," and one simply finds ways to manage the pain and control the symptoms. Interim surgeries to remove local lesions and clean up the damage to adjacent organs, birth control to regulate the period, pregnancy to halt the monthly menstrual flow for a more extended period of time, and, as a last resort, hysterectomy – these were what I was told were viable options to manage this affliction.

I was believing that I had trauma, pain, and potentially endless surgeries to look forward to during my teenage years and, thereafter, was a terrifying prospect for a young girl. Highly creative and expressive, happy, outgoing, and vivacious, I remember looking toward the frontier of my life somehow much less enthusiastically than I'd been prior to the diagnosis. I saw how my mother's not-fully-understood experience created friction between my parents – so many subtle nuances to the extreme discomfort that were complicated to translate in language.

Like most young girls, I dreamed of having boyfriends and a thriving career someday. Academically, I was extremely focused and excelled. As my nature was inquisitive, I had endless questions: "How would I *ever* date boys, or even focus on a profession if I'd intermittently, and likely often, be out of commission?" In my mind, I began associating myself with being a victim, compulsively envisioning the

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limitations and downtime associated with either being in surgery or healing from a queue of surgical procedures: "What about my sexual organs? Would they function properly? Would intercourse be painful? Would I be able to have children? What kind of a man would be interested in a woman who couldn't enjoy sex or have children?" I began rejecting myself the moment I received the "verdict." I began to loathe the very idea of womanhood. This that I once looked forward to had, in a flash, become a curse.

Part of what made the process so emotionally and psychologically jarring was that I was still a virgin, and yet even before ever having my period, I would fly regularly to Atlanta for gynecological visits. It felt so weird to have foreign objects probing inside of my vagina in the form of ultrasounds, and speculums, when a penis had never even been inside of me. Although my mother was always present in the visits, and my endometriosis specialist treated me with the ultimate tenderness and kindness, I was confused and hurt – hurt by God. I felt betrayed.

Although I recall peripheral murmurs of endometriosis at age 11, it wasn't until I turned 16 that my first laparoscopy was scheduled. Prior to this, I'd been put on birth control to regulate my menstrual cycle – an unwelcome side effect was substantial weight gain. Imagine, a waif of a teen, suddenly 20 plus pounds heavier in a matter of weeks. Sure, the larger breasts were a nice perk, but I clearly recall my doctor informing me that if I continued down "that" path, I'd be in big trouble with my health. I was scared. Intending to find the best balance of hormones, I was prescribed a new set of birth control pills and then another and another.

I felt heavier, not only physically but also psychologically and spiritually. I felt darker, and I didn't understand the accompanying extreme emotional swings. For someone who had always been seen as "light and free," it now felt as if this weighty shadow followed me wherever I went. I became angry at the illness. When those close to me were astute enough to realize that the extreme shift in disposition was a direct result of the physical pain, a common phrase was, "Your endometriosis must be acting up." "*My* endometriosis?! Why do I have to own this? Why is this deemed mine? Because some doctors gifted me the label? I don't want it. I don't even want to be associated with it. Please, God, take it away from me!" I would plead. "I just want to be a normal, happy, teenage girl!"

The unfortunate truth was the energy of depression and feeling powerless to my diagnosis was beginning to take its toll. I found it challenging, even humiliating, to articulate what I was feeling or to even realize that not all beings are subject to this sort of trauma. I was often quiet, introverted, suffering alone with my discomfort, until it would reach a crescendo and I could no longer be. At the breaking point, it felt as if a force greater than myself would suddenly rise up, causing me literally to drop to my knees, begging for the pain to abate.

As the endometriosis grew, I had a hard time simply being. Days before my cycle, intense cramps would ensue, followed by a violent, extremely bloody, clot-laden period. There were times I was in so much pain that I literally could not get out of bed – where to move my pelvis even slightly felt like my insides were being stabbed incessantly. When the quality of the internal tumult was so extreme, the only way to quell the pain in order to function was to take medication. Sometimes

even strong, prescribed narcotics did not begin to touch it. What I discovered with endometriosis is that it is insidious – a shape-shifter – and often goes subtly underground for stretches of time. This leaves one with the false hope that it has all but vanished, only until, for no apparent reason, it becomes triggered, returning with a vengeance.

Days after my sixteenth birthday, I found myself with profound rectal "shooting pains" that had me incapacitated. I left summer camp prior to the end of session to fly to Atlanta for an urgent first surgery at Northside Hospital. The discomfort post-op was inexplicable. During the procedure, air had migrated upward and had become trapped deep in the tissues surrounding the shoulder blades. This was perhaps the most physically disturbing aspect of postoperative recuperation. My organs were swollen and belly distended, which meant that I had to wear men's drawstring pants to accommodate the inflammation. Jokes about the fashion police only exacerbated my sense of humiliation. We all know that in our teenage years, we just want to fit in. I felt that I stood out for all the wrong reasons, and it made me feel even more separate from my peers.

My inner rebel began taking root at this point: disillusionment with rules, authority, "the establishment," and a feeling, whether real or imagined, of being different than and segregated from my friends. I was instructed to use a rolling backpack (the true make of an absolute nerd!) and to refrain from exercise. To say that it felt like lead weights had been dropped into my center would not be an exaggeration. Not only did my physicality feel sluggish, my mind did as well. I had a deep *belief* that the girl who once had great luck was now on the receiving end of quite the opposite: "I remember the former me. Where had she gone? What happened to her?" Although I always had an incredible capacity for positivity and resilience, these thoughts lived under the surface. I wanted to expedite the healing the same way I witnessed my father expedite orders in his business, but even more so, I wanted complete healing, and this kind of healing cannot be rushed. This would be a lesson in acceptance I would need to learn.

Although my body came into a sense of greater harmony post surgery, I understood that it was only a matter of time before the inevitable "next wave" would come. It was as if a foreboding presence was always lurking just around the corner. Cleared from one area, if the root cause is not addressed, endometriosis migrates to another.

When I was finally allowed to begin dance class, I was fortunate that my teacher placed an emphasis on the mind-body-spirit complex, subtly integrating yogic principles. The foundation was in honoring our individual form, wherever we were at, on any particular day. My teacher demonstrated safely pushing ourselves beyond our comfort zone, which for me, a deep understanding of the comfort zone versus breaking point was the razor's edge. In retrospect, this modern dance class was an integral part of my initial healing because it encouraged my body to move in natural, feminine ways, in spite of a feeling of deep-seated stuckness.

The feminine energy within all of us, when out of balance, will express through great distress. Whether we inhabit a male or female body, what this part really desires is sensitivity, love, and kindness. This is the creative principle that is longing

to express our innermost desires. We busy our days with self-rejection, hyperfocused on perceived flaws and shortcomings. This is the case with most teens and humans in general. We do not allow ourselves the opportunity to rest – truly rest – within our bodies. In order for the deepest healing to occur, we must let go of contractions on a cellular level. We must open up and relax the clamping down, the holding fast to antiquated beliefs that no longer serve our well-being. When we believe that "there is something wrong with me," we quite literally communicate and affirm this belief to the universe, *and* if we give it our energetic buy-in long enough, it will eventually manifest.

I can see now that a visual arts class would have been invaluable at the time because it would have afforded the opportunity to externalize the monster in the mind. It is through the arts, journaling, storytelling, music, dance, and many other forms of movement and creative expression that we are able to connect with, understand, make peace with, and release these dark, contracted beliefs and energies we hold.

These energies are not to be demonized. They are intended to lead us to the source of our misalignments so that we may shift in positive directions and heal ourselves. Afterall, any expression of original art comes from the source within. Perhaps with these tools, I would have realized that this disease "haunting" me and "chasing" me was being created and recreated due to my fear of it. This is not to say that I would not and could not still have aspects of endometriosis manifest; that said, it would be wise for all women dealing with endometriosis to have creative outlets.

Fortunately, I was a proficient writer and performance artist. If only I had understood at that time when I brushed up against feelings of "I can't" while singing: "I can't reach that note; I can't belt hard enough, strong enough" – if only I had understood that it is this false belief of "I can't" that created the very feeling of pressure, anxiety, and distress in the body. This "I want to so badly but I can't," in turn, was the same energy locked at the root of the "I can't. I'm not good enough. I'm small and limited. I don't deserve it" programming. Our words, spoken aloud or internally, are powerful. Repeated, and unexcavated, they create our beliefs and our feelings. It is these negative words, thoughts, and feelings that become our beliefs, which prevent us from realizing the truth – that "we can overcome anything and that we are not victims to anyone or anything" – including endometriosis.

In these modern times, no story would be complete without the clear articulation and understanding that what I share here – my personal experience with endometriosis – is, indeed, a story. This is not to deny circumstances as they arise and unfold but rather to reveal that the lesson inherent in my journey with endometriosis was the eventual awareness that thoughts do indeed become things as mind literally creates everything. In a sense, this walk through endometriosis became my personal awakening as it was the entry point into the depths of consciousness by which I was able to begin exploring the stunning supercomputer that is the mind. What we input whether on a conscious or subconscious level, mind outputs. It is a most obedient servant. What initially seemed a curse became the very portal into the possibility, and eventuality, of an ever-expanding personal self-mastery.

I came to see firsthand – to know beyond any shadow of a doubt – that the beliefs and fears we hold in mind regarding our future quite literally manifest our circumstances in the here and now. These beliefs, whether conscious or subconscious, are based on outdated information from the stale past. I began to watch carefully and firsthand came to notice how prior experiences, and our individual interpretations of those experiences, greatly impact our current life situation. Additionally, I understood how ancestral and core family histories, as well as cultural, social, religious, economic, and a multitude of other factors, influence our worldview, which, in turn, cycles "round to form our own thoughts and belief systems."

Realizing that my inner world was, in essence, creating my life experience on every level, I recognized that the only true solution to disentangle from this sticky "disease" was to embrace it fully, shining the light of awareness upon it. I needed to understand what the foundation of this malady was. What was the purpose of this challenge in my life? It became apparent that if I could "get to the root" of which beliefs held in the mind had created the disease in the body, perhaps I could free myself from feeling enslaved and a "victim" of this label: "endometriosis." I made a firm decision to engage a self-orchestrated experiment to unlock the keys to the very programming that allowed this illness to persist. I chose to love it into submission or, in the very least, remission. I was willing to welcome endometriosis as my teacher. The teachings that ensued were far greater than I ever anticipated.

When I was first approached with the opportunity to contribute my story, I will admit there was a moment of pause and reluctance. I wanted to ensure that my sharing would not perpetuate a sad, depressing story of a lifelong sentence labeled "endometriosis" but rather serve to illuminate the limiting beliefs held within the consciousness of women living with endo (who continue to perpetuate the disease in themselves as well as the collective). Instead of solely sharing my history with it, my intention is to bring a voice to the inner world of those diagnosed and/or suffering but still undiagnosed, to shed a light on some of the thought patterns that are common in women with endometriosis, to reflect and mirror to these souls that they are not alone, and to encourage more and more women to find the courage to rise above feeling a victim trapped inside an ailment.

For myself, I discovered that even the most heinous of negative thoughts about the future became quickly incinerated by the belief "I will overcome. I can." When we recognize that we are not powerless to a diagnosis outside of ourselves, as its origins emanate from within, we are able to rewire and reprogram our body-mind-spirit complex to embrace life and, ultimately, our feminine parts. The opportunity, for me, was to awaken to my capacity to heal myself through vigilant self-awareness.

Because endometriosis is something lived with, it's about recognizing one's innate sensitivity and coming to know one's own body so integrally that when things come out of balance, even slightly, we are astute enough to nip it in the bud. It's about discovering the skills and tools in the form of holistic living, and employing them to empower authentic health, through practices that open blockages and create an unbridled vital flow of energy for our highest well-being. So here is where I take the writer's pen back into my own hand and script a new story – a story of joy,

freedom, and inspiration from feeling a victim. We all have the capacity to rewrite our story – to edit and reedit it. Although the timeline may appear to be linear, it is not, and things that seem to be our greatest afflictions turn out to be our gateways to liberation. It is a choice, as well as our birthright, to fully embrace the art of healing in its myriad expressions and release all resistance to it. After all, *that* is the purpose of this human experience.

Part X
Pre-operative Considerations

Chapter 32
Anesthesia Considerations for Operative Laparoscopy in Pediatric and Adolescent Gynecological Surgery

Katie Roddy, Shivani Gupta Mukkamala, Erin V. Rosenberg, and Chhaya Patel

Introduction

The advent and improvement of laparoscopic surgical techniques have led to expanded surgical and diagnostic indications for this technology in the pediatric patient. Some of these benefits include smaller incisions, less fluid and heat loss, less retraction of tissues, better visualization of difficult areas due to the use of cameras, improved cosmetic scar, earlier postoperative mobilization and recovery, shorter post-op ileus and earlier oral intake, fewer respiratory and wound complications, less post-op pain, and earlier discharge. Laparoscopic procedures are frequently performed for diagnostic and therapeutic purposes in gynecology. The common procedures including congenital anomalies, such as Mullerian anomalies, disorders of sex development, and adnexal masses, such as ovarian torsion, tumors,

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or tubo-ovarian abscess, are also diagnosed and treated with laparoscopy. Other frequent indications include diagnosis and treatment of endometriosis, pelvic inflammatory disease, and procedures to preserve ovarian function before pelvic irradiation [1].

Physiologic Changes During Laparoscopy

Most physiologic changes in pediatric laparoscopic surgery are a result of the creation of a pneumoperitoneum with carbon dioxide (CO2) which is necessary for optimal surgical exposure. Also, extremes in patient positioning, most commonly Trendelenburg position, can significantly contribute to further alterations in physiology. Although these changes are usually tolerated well unless significant cardiovascular or respiratory comorbidities are present, they can cause significant cardiovascular, respiratory, and neurologic effects [2]. Care of the patient by a pediatric anesthesiologist with an intimate knowledge of pediatric physiology is recommended.

Respiratory System

During abdominal gas insufflation, the intra-abdominal pressure (IAP) increases, causing a correlative rise in peak inspiratory pressure (PIP). This may result in hypoventilation and hypercapnia from decreased tidal volume (TV) delivery. Additionally, this decrease in diaphragmatic excursion causes atelectasis and decreased functional residual capacity (FRC) leading to intrapulmonary shunting and hypoxemia [3]. This alteration in physiology may require a change in the previously set mode of ventilation from volume control (VCV) or pressure control (PCV) to pressure control-volume guarantee mode (PC-VG) in order to maintain adequate minute ventilation (MV) while minimizing dangerous increases in PIP that cause barotrauma. Positive end-expiratory pressure (PEEP) can maintain alveolar patency to some degree, helping to reestablish FRC. Additionally, pneumoperitoneum causes cephalad migration of the diaphragm, which may lead to endobronchial intubation. This is exacerbated in steep Trendelenburg position. Endobronchial migration of the endotracheal tube (ETT) should be quickly diagnosed if there is an abrupt increase in PIP, decreased TV delivery, decreased exhaled (end-tidal) carbon dioxide (ETCO2), and diminished auscultation of lung sounds unilaterally.

As insufflation pressures needed for surgical visualization change, it is prudent to adjust ventilator settings to prevent wide swings in PIPs. When initial Veress needle entry for gas insufflation is performed, the insufflation pressure needed may

be higher as the trocars are being placed. This is done to increase the distance between the abdominal wall and underlying structures during non-visualized trocar insertion, in attempt to prevent damage to intra-abdominal organs and vasculature. In the absence of comorbid conditions such as cardiovascular or respiratory disease, most children can tolerate transient increases to 20–25 mm Hg for safe trocar placement [4]. Once access to the peritoneal cavity is assured, pneumoperitoneum is established based on IAP rather than volume of gas [4]. Children can tolerate 8–10 mm Hg, whereas adolescents can tolerate 10–15 mm Hg.

Cardiovascular System

Pediatric patients absorb CO2 at a much faster rate given their greater peritoneal absorptive area to body weight ratio and shorter distance between capillaries and peritoneum [2]. As insufflated CO2 is absorbed into the bloodstream, it is likely necessary to increase MV to maintain normal arterial CO2 levels in order to avoid consequences of hypercapnia. Hypercapnia results in stimulation of sympathetic nervous system activity, leading to an increase in blood pressure, heart rate, myocardial contractility, and arrhythmias [2]. Additionally, hypercapnia causes myocardial sensitization to catecholamines, particularly when volatile anesthetic agents are used. The additional CO2 load can lead to hypercapnia in the postoperative period because large quantities can be buffered by body tissues [2]. As CO2 is excreted postoperatively, this increases the risk of apnea, which is exacerbated by the lasting effects of anesthetic drugs and diaphragmatic dysfunction in the immediate post-op period.

Cardiovascular physiologic response to elevated IAP is secondary to inferior vena cava (IVC) compression, which decreases venous return and increases systemic vascular resistance (SVR), which may decrease stroke volume and cardiac output (CO). In most cases, arterial blood pressure is maintained or increased. In adults, if IAP is kept below 15 mm Hg, venous return is actually augmented as blood is forced out of the splanchnic venous bed, increasing CO [2, 5, 6]. However, in children, IAP as low as 12 mm Hg has been associated with both decreased cardiac index and left ventricular hypokinesis [5].

Because children have a higher resting vagal tone, this poses a greater risk of reflex bradycardia in response to insertion of Veress needle or trocars, peritoneal stretch by creation of pneumoperitoneum, or CO2 embolization [7–10]. Other bradyarrhythmias, such as atrioventricular dissociation, nodal rhythm, and even asystole, have been reported [9, 10]. Direct communication to the surgical team and release of pneumoperitoneum should occur, and if ineffective, prompt treatment with anticholinergic and sympathomimetic drugs, such as glycopyrrolate, atropine, or epinephrine, may be indicated if hypotension ensues or if bradycardia is

prolonged [11]. After resolution of bradycardia, slow reinsufflation using lower IAPs to maintain pneumoperitoneum or conversion to open procedure may be necessary.

Central Nervous System

Adverse neurologic side effects of increased IAPs include increased intracranial pressure (ICP) and decreased cerebral perfusion pressure (CPP). This is also exacerbated by hypercapnia, elevated SVR, and Trendelenburg position. Due to these negative physiologic changes, it is inadvisable to perform laparoscopic surgery on patients with reduced intracranial compliance unless absolutely necessary [12].

Preoperative Evaluation

A detailed history and physical examination should be performed for elective or emergency laparoscopy. Preoperative cardiovascular and respiratory system function will predict the success of the laparoscopic procedure. For the most part, this patient population is healthy and requires minimal, if any, laboratory testing. A complete blood count and pregnancy testing should be performed when indicated. Patients undergoing laparoscopic gynecologic operations tend to be low risk for bleeding. If bleeding is anticipated, a type and cross should be sent preoperatively, and larger-bore intravenous access should be placed. Diagnostic studies should be ordered according to the requirement of the type of procedure and coexisting diseases.

Preoperative Fasting

The accepted practice guidelines based on the American Society of Anesthesiologists (ASA) for preoperative fasting to reduce the risk of pulmonary aspiration are 2 h for clear liquids; 4 h for breast milk; 6 h for formula, nonhuman milk, and light meal; and 8 h for a fatty meal [13]. It should be noted that interpersonal variation in residual gastric volume exists [14] and that a more conservative approach for patients presenting with diagnosis of gastroesophageal reflux may be required. The evidence for liberal fluid intake prior to surgery is gaining popularity in this patient population. Children who have been permitted fluids up to 2 h preoperatively have a more comfortable experience in terms of hunger and thirst [15]. Fasting policy can be reinforced by a preoperative reminder in appropriate candidates via a telephone call the night prior to surgery.

Preoperative Pregnancy Testing

Pregnancy testing policies require ethical, logistical, and legal considerations. Depending on the studies, the incidence of undiagnosed pregnancy varies. Concerns include the risks of congenital malformation, spontaneous abortion, and medical-legal risks. It may be difficult obtaining an accurate history from the adolescent female, even in the absence of parents. Most centers have established a policy for preoperative pregnancy testing for female patients of childbearing age. A signed waiver of testing would be obtained in case of refusal of testing or inability to obtain a urine specimen for pregnancy testing on the day of surgery. A support structure including social worker and referral ability should be available if testing is performed.

Premedication

There is no consensus among experts about the value of routine pharmacological premedication in the ambulatory setting due to the possibility of an extended sedative effect delaying patient discharge. The most commonly used compound for premedication is midazolam; it reduces anxiety and improves the quality of behavior at induction. Oral midazolam is the most commonly used agent and benefits from a relatively rapid onset and reliable effect. An oral dose of 0.25–0.5 mg/kg should be administered 20–30 min prior to taking the child to the operating room. Intranasal dose of 0.15–0.2 mg/kg can also be used. Intranasal dexmedetomidine dose of 1–3 mcg/kg has also been used successfully. It causes preoperative sedation and an improved recovery profile. Alternative pharmacologic agents are oral ketamine (5 mg/kg) or fentanyl (15–20 μg/kg) even though these agents are sometimes associated with prolonged recovery (ketamine) and nausea, vomiting, and pruritus (fentanyl). Child life specialists and distraction techniques such as preoperative coloring books, stories, video games, and websites may be used to help children of all ages learn about surgery and anesthesia and may permit children to cooperate. Outpatient surgery presents a unique opportunity for parental presence at induction largely due to the healthy patient population. Parental presence at induction may increase cooperation and parental satisfaction with the perioperative experience. However, parental presence at induction remains controversial due to lack of evidence supporting the reduction in patient anxiety. The most current evidence does not support parental presence at induction of anesthesia because it does not reliably alleviate the anxiety of either the children or parents [16]. Video games on phones or other mobile devices have been shown to reduce preoperative anxiety and improve patient cooperation with induction of anesthesia [17].

ERAS (Enhanced Recovery After Surgery)

Enhanced recovery after surgery (ERAS) is a multimodal approach to the care of the surgical patient focused on reducing the stress response and associated physiologic changes that accompany surgery in order to improve recovery, reduce postoperative morbidity, and decrease overall costs. ERAS protocol includes perioperative patient education, shortened preoperative fasting durations, minimally invasive surgical techniques, opioid-sparing analgesia, and early postoperative oral feeding and mobilization. These interventions theoretically maintain physiological homeostasis and minimize surgical stress, thus facilitating a quicker return to baseline [18]. Over the past 20 years, ERAS programs have been found to result in reduced length of stay and complications in adult patients. Despite abundant adult literature describing implementation and outcomes of enhanced recovery programs, pediatric data in this area is sparse. There is some literature of successful implementation for general surgery and urological procedures in pediatric population. This limited literature available indicates that ERAS would be safe and potentially effective for pediatric and adolescent gynecological surgery [19]. However, more studies are needed to assess the efficacy of ERAS in gynecological surgery.

Induction

General anesthesia with endotracheal intubation is the preferred anesthetic technique in pediatric patients undergoing laparoscopy. Younger patients with fear of preinduction intravenous placement may have a safe inhalational induction via mask [20]. Inhalational technique with a balanced mixture of nitrous oxide and sevoflurane has been safely employed. Post induction of general anesthesia, intravenous access should be secured [2]. Should the patient be an adolescent, obese, or suffer from nausea and vomiting, they can have a preoperative intravenous placement with intravenous induction. Intravenous access can be made comfortable with use of Eutectic Mixture of Local Anesthetics (EMLA) cream or nitrous oxide (in non-nauseous patients). Rapid sequence induction is preferred in a patient with active nausea and vomiting to prevent aspiration of gastric contents during induction. The technique for induction should be left to the anesthesiologist's judgment.

Maintenance Anesthesia

Maintenance of anesthesia can be achieved with a variety of anesthetic drugs. Generally, most anesthetics follow a balanced technique with a combination of potent volatile agents, sevoflurane, desflurane, or isoflurane, and intravenous agents including hypnotics and opioids [6]. Female patients undergoing laparoscopic

operations have higher likelihood of postoperative nausea and vomiting (PONV) [21], and measures should be taken to avoid medications that increase probability of complications. Potent volatile agents, nitrous oxide, opioids, and reversal agents of non-depolarizing agents have all been implicated in increasing nausea and vomiting. Using multimodal pain management techniques including minimizing opioids has been associated with decrease in postoperative nausea and vomiting. Total intravenous anesthesia can also be selected for maintenance in patients with severe postoperative nausea and vomiting [22]. Spontaneous ventilation is generally not preferred for laparoscopic procedures and non-depolarizing neuromuscular blocking agents can also be used for maintenance of general anesthesia. After the procedure is completed, the muscle relaxant must be reversed. Neostigmine can be used in conjunction with glycopyrrolate. Neostigmine has been associated with PONV; however, the risk of postoperative weakness and ventilation outweighs the risk of not reversing. A newer agent, sugammadex, a modified cyclodextrin to encapsulate steroidal NMB, has also been used to reverse agents without the risk of PONV. Sugammadex interacts with progesterone found in oral contraceptives and hormonal intrauterine contraceptive devices. Patients must be notified of decrease in efficacy of their contraception. A dose of 4 mg/kg has been predicted to decrease progesterone exposure by 34% [23, 24]. This poses a unique ethical challenge in pediatric patients as patients can be sedated postoperatively from anesthesia and opioids, and their parents in certain states cannot be part of a discussion on contraception.

Use of nitrous oxide has been controversial, and a balanced approach should be taken. Nitrous oxide has been associated with higher incidence of PONV than other inhalational agents [25]. Nitrous oxide can diffuse into air containing spaces over time and lead to bowel distension. Based on small studies, N_2O does not appear to affect distention during short laparoscopic procedures [26]. However, in a study of 350 patients who underwent colon surgery for 3–3.5 hours, surgeons were blinded from the technique. Moderate or severe bowel distention occurred in 23% versus 9% in cases with N_2O [27]. Children can absorb N_2O quicker than adults and judicious use should be considered. A short period of exposure during induction for second gas effect should not distend the bowels.

Monitoring

The ASA has mandated standards for basic anesthetic monitoring [28]. Pediatric and adolescent patients undergoing anesthesia should be upheld to the same standards. During all anesthetics, the patient's oxygenation, ventilation, circulation, and temperature must be continually evaluated.

For laparoscopic procedures, endotracheal intubation is highly recommended. The endotracheal tube provides airway protection and enables sufficient ventilation in patients with increased IAP. Continuous monitoring for the presence of ETCO2 should be done to ensure adequate ventilation. This is achieved with capnography

or capnometry [28]. As previously discussed, during abdominal insufflation, it is prudent to closely monitor PIP as the exhaled TV may decrease significantly from a reduction in pulmonary compliance secondary to increased IAP. This may require modification to ventilator strategies in order to maintain normal CO2 levels. Additionally, as the PIP increases, a leak may develop around the ETT cuff that was not present prior to insufflations [6]. This requires further instillation of air into the cuff to ensure adequate TV delivery.

To ensure adequate blood oxygenation, a quantitative method, such as pulse oximetry, should be utilized. Additionally, inspired oxygen gas analysis is done to prevent the delivery of a hypoxic gas mixture, which may occur in the event of rebreathing, the result of an expired or saturated CO2 absorbent.

Continuous electrocardiogram (ECG) and heart rate monitoring with frequent interval measurement of noninvasive blood pressure should occur at least every 5 minutes to ensure adequate circulation. Rarely, invasive arterial blood pressure monitoring is needed for laparoscopic endometriosis surgery.

A naso- or orogastric tube may be placed after induction in order to decompress the stomach to aid in optimal surgical exposure and pneumoperitoneum. Similarly, a Foley catheter should be placed prior to the start of surgery to further improve surgical visualization by decompressing the bladder and allow for precise urine output measurement for more precise fluid management.

Due to their smaller body size, pediatric patients may be positioned relatively further away from the anesthetic team in order for more optimal surgical positioning and exposure. This lends to decreased accessibility, preventing intermittent cardiorespiratory examination by the pediatric anesthesiologist. Precordial and esophageal stethoscopes allow for continuous heart and lung auscultation. This is primarily important during abdominal gas insufflation or in the Trendelenburg position. The pneumoperitoneum moves the diaphragm and mediastinum more cephalad, which may lead to endobronchial or main stem intubation, a well-recognized complication [29].

A peripheral nerve stimulator should be used to monitor the level of neuromuscular blockade throughout the procedure aiming for the least degree of block necessary for the clinical situation. A 2018 meta-analysis of randomized controlled trials that compared deep with moderate neuromuscular block during laparoscopy found insufficient evidence to support the use of deep neuromuscular blockade [30]. Discussion with the surgical team regarding the level of muscle paralysis is advised.

Positioning

Patient positioning may vary depending on the planned procedure. If vaginal exam or uterine manipulation is required throughout the procedure, many adolescents can be positioned in dorsal lithotomy using standard or pediatric Allen stirrups. For younger pediatric patients with shorter limb length who cannot be accommodated

with stirrups, a supine position with the legs in a modified lithotomy or frog-leg position allows for access to the vagina intraoperatively [31]. A combination of gel rolls, towels, foam padding, and tape can be used to bolster the legs in a frog-leg position. This is important to prevent excessive hip abduction (>90 degrees) and external rotation, which may cause femoral nerve injury [32].

Pressure points, including elbows, hands, heels, sacrum, and intravenous (IV) tubing hubs, should be adequately padded prior to draping the patient. This is achievable with foam egg crate arm pads or cradles. Due to the short stature of pediatric and adolescent patients, the distance between the patient's outstretched arms and abdomen may not be adequate for the surgeon's mobility during the operation. Outstretched arms also lend to inadvertent leaning by the surgical team, which may cause nerve injury or IV compression [33]. Thus, the arms usually require tucking at the patient's side with thumbs oriented superiorly in military position to avoid ulnar nerve compression [33, 34]. It is advisable to ensure that a neutral position of the patient's shoulders is maintained. Excessive cephalad or caudal traction may occur with tucking the arms or with bed tilting, especially if Trendelenburg is required [34].

Rarely, the pediatric anesthesiologist would unexpectedly require access to the arms intraoperatively for additional IV placement. This may occur only during the event of infiltration of an existing IV or rapid, uncontrolled blood loss. It is also likely that IV access will be in the upper extremity, which requires routine evaluation to prevent fluid and medication infiltration. Optimally, visual inspection of the IV site is done every hour or earlier if malfunction is suspected.

For improved surgical exposure, the lower half of the operating table may have been dropped. At the case conclusion, it is crucial to protect the patient's fingers from entrapment, crush, or even amputation injury when the table is rearticulated [33].

Nerve Injury

It is difficult to confirm the incidence of postoperative nerve injury caused by gynecologic laparoscopy. This is likely due to underreporting as most neuropathies self-resolve over time [32]. Although nerve injury due to malposition after gynecologic laparoscopic surgery is uncommon, it is essential to minimize iatrogenic causes. The major causes are poor patient positioning while under anesthesia, improper use of stirrups or stirrups with inadequate support (i.e., "candy cane" leg supports), inadequate protection of superficial nerve regions, long operative time, and closure of lower lateral port trocar insertion sites [32, 35, 36]. In one large retrospective review including over 198,000 patients, it was noted that for each hour in the lithotomy position, there was a 100-fold increased likelihood of nerve injury [37].

In adults, the estimated incidence of nerve injuries associated with malposition under anesthesia during gynecologic laparoscopy ranges between 0.02% and 0.16% in the upper extremities [38, 39] and between 1.5% and 1.8% in the lower extremities [38]. A prospective cohort of 616 female patients who underwent elective gynecology surgery was conducted to evaluate the incidence and prognosis of postoperative neuropathies of the lower extremity. The overall incidence of nerve injury was 1.8%. The most frequent nerve injuries were the lateral femoral cutaneous nerve of the thigh and the femoral nerve [38]. Complete resolution of neuropathic symptoms occurred in all but one patient (91%). Median time to resolution of symptoms was 31.5 days (range 1 day to 6 months).

Brachial plexus nerve injuries although uncommon may be the most serious of all nerve injuries related to improper positioning of the patient during laparoscopic gynecological surgery. Brachial plexus stretching and ischemia may be caused by hyperabduction of the arms, external rotation, and posterior shoulder displacement [40]. Additionally, direct compression of the plexus may result from placing shoulder braces too medially causing downward displacement of the humeral head and clavicle which acts as a fulcrum on the brachial plexus [41].

Peripheral nerve injuries of the upper extremity (UE) usually occur because the superficial anatomical position of the nerve makes it more prone to direct compression between bone and a hard surface, such as the operating table. Most UE nerve injuries can be avoided with proper padding of the elbows and arms [32–34]. See Table 32.1 for a summarized approach to nerve injury and prevention strategies.

Perioperative Fluid Management

Perioperative fluids should be adapted to the patient status, the operation, and the expected events in the postoperative period to maintain a correct fluid and electrolyte balance and normal cardiovascular stability [42]. Most of the fluid during the perioperative period is needed for replacing either fasting deficit or third-space losses. Since both losses are mainly extracellular fluids, solutions should have sodium and chloride and a low concentration of calcium, bicarbonate, and potassium making lactated Ringer's an ideal solution [43]. Minimal blood loss can be replaced with isotonic fluids. More hemodynamic significant bleeding can be replaced with colloids such as albumin, or in severe bleeding, blood products such as packed red blood cells can be used.

Teamwork and Communication

Given the complexity of intraoperative adolescent care for laparoscopy, teamwork and good communication between the surgeons, anesthesiologists, and nurses are vital to improving outcomes, minimizing complications, and improving efficiency.

Table 32.1 Nerve injury mechanism and prevention in gynecologic laparoscopy

Nerve injured	Mechanism of injury	Prevention technique
Radial nerve (C5–T1)	Compression between the edge of the operating table and the humerus (as the radial nerve passes over the humeral spiral groove)	Avoid positioning the arm at edge of the arm board or edge of operating table; adequate padding of medial arm
Ulnar nerve (C8–T1)	Persistent pressure on the medial epicondyle of the elbow during arm positioning; prolonged or extreme elbow flexion	Adequate padding over the posteromedial elbow. If arms extended on boards, keep arms supinated (with palms facing toward the ceiling). If arms tucked at patient's side, keep arms pronated (with palms facing inward and thumbs pointing superiorly toward the ceiling)
Upper brachial plexus nerve roots (C5–C6)	Hyperabduction of the arms >90 degrees (magnified by arm pronation and head rotation away from the arm)	Tuck pronated arms at patient's sides, keep head centered, and supinate the extended arms
Lower brachial plexus nerve roots (C8–T1)	Steep Trendelenburg position 30–40 degrees (magnified by extended arms and the use of shoulder braces which cause downward displacement of the humeral head and clavicle acting as a fulcrum on the brachial plexus, causing stretch injury); direct compression on brachial plexus	Minimize the angle of inclination in Trendelenburg position, and avoid the use of shoulder braces If shoulder braces must be used, apply them to the acromioclavicular joint (laterally), and pad adequately with foam, egg crate, or gel pads
Femoral nerve (L2–L4) Lateral femoral cutaneous nerve (L2–L4)	Prolonged hip flexion, extreme abduction, and external rotation (causes stretching and entrapment of the nerve under the inguinal ligament, interrupting adequate blood supply to the nerve); compression by inadvertent leaning on the patient's thigh [57, 58]	Proper positioning in the lithotomy position with limitation of hip flexion, abduction, and external rotation. Minimize length of time needed for lithotomy
Common peroneal nerve (branch of sciatic nerve)	Compression between the head of the fibula and a hard surface (such as candy cane stirrups); prolonged knee flexion with excessive hip external rotation	Adequate padding of the knee area especially if touching hard surface. Avoid use of candy cane stirrups. Appropriately sized Allen stirrups should be used instead. Avoid excessive knee flexion and external rotation of the hip

Postoperative Considerations

The recovery room should be equipped with the tools and personnel capable of managing crisis. The personnel involved must be trained in pediatric care and have familiarity with the specific problems encountered in this unique population. Nursing and medical personnel should be certified in Pediatric Advanced Life

Support. A patient with postoperative concerns after anesthesia or surgery must be approached in a systematic fashion, using medical history, clinical findings, and laboratory evaluation to rapidly identify and appropriately manage the most likely cause. The safety and adequacy of postoperative anesthesia care is highly dependent on the immediate availability of skilled help. In case of a major adverse respiratory or cardiac arrest, a code procedure must be in place in order to quickly recruit sufficient and pertinent support.

Cardiac arrest in healthy children is rare. The most common recovery issues include postoperative pain, airway and pulmonary complications, nausea and emesis, temperature abnormalities, and delayed emergence [44, 45].

Pain Management

Pain remains one of the most frequent complications after surgery. Pain following laparoscopy results from rapid distension of the peritoneum, visceral manipulation, irritation and traction of vessels and phrenic nerves, presence of residual gas and inflammatory mediators, and unusual positions that can stretch nerves [46, 47]. Pain management is vital in pediatric patients undergoing outpatient surgery and must include parental education regarding the assessment of their child's pain and analgesic needs following discharge. The analgesic plan should be considered before incision and once again prior to emergence. Preoperative analgesic administration is an effective way of preventing postoperative pain. An analgesic plan should take into consideration a multimodal approach that includes non-opioids, opioid analgesics, adjuvants such as alpha-2 agonists (dexmedetomidine), and regional and local anesthetic techniques when suitable for the patient. Commonly used opioid-sparing NSAIDs in the pediatric ambulatory setting are summarized in Table 32.2. Local anesthetics can be injected intraperitoneally as well as infiltrated on the puncture sites [46]. The use of caudal, epidural catheter, and bilateral rectus sheath block has

Table 32.2 Commonly used opioid-sparing analgesics in pediatrics

Generic name	Band name	Dose mg/kg frequency	Maximum daily dose
Acetaminophen	Tylenol ® Tempra® Ofirmev®	10–15 PO q 4 h 25–40 PR q 8 h 12.5 IV q 4 h	4000 mg/day 60 mg/kg/d preterm 80 mg/kg/d term 90 mg/kg/d older
Ibuprofen	Motrin ® Advil ® IV form: Caldolor®, NeoProfen®	5–10 PO, IV q 6–8 h	3200
Ketorolac	Toradol®	IV or IM load 0.5 Maint 0.2–0.5 q 6 h PO 0.25	120

also proven beneficial. NSAID can be given in oral, rectal, intramuscular, and intravenous routes. Ketorolac and ibuprofen are intravenous NSAIDs available in the United States. The current recommended dosing for ketorolac is 0.25–0.5 mg/kg every 6 hours. Ketorolac provides postoperative analgesia that is comparable to opioids in children of all ages. It lacks opioid side effects such as respiratory depression, sedation, nausea, and pruritus, making it a very attractive choice for the treatment of postoperative pain. Multimodal, opioid-sparing analgesic techniques also decrease perioperative respiratory complications. The PACU (Postanesthesia Care Unit) orders should include clear doses and intervals for administration of pain medications. The instructions should also include information on whom to contact in the event of unrelenting pain and when to seek emergency medical treatment.

Postoperative Nausea and Vomiting (PONV)

Laparoscopy and gynecological surgery have been identified as a risk factor for PONV; therefore, routine prophylactic multimodal antiemetic therapy should be utilized in all patients undergoing laparoscopic surgery [47]. Prevention of PONV is an important aspect of any anesthetic. PONV is a particularly troublesome problem following laparoscopy surgery in the ambulatory setting where associated delays in discharge and possible hospital admission can drive up costs. Appropriate efforts to reduce the incidence of PONV in the pediatric population are crucial to the success of anesthesia program. Because nausea is difficult to diagnose in the pediatric population, only active vomiting is typically studied and treated. A combination of drugs including 5-HT3 receptor antagonists (ondansetron and granisetron), steroids (dexamethasone), antihistamines (promethazine, diphenhydramine), and metoclopramide is commonly used for PONV. Typical dosing for these medications is shown in Table 32.3. The safety and efficacy profile of ondansetron makes it the ideal choice for prophylaxis and treatment of PONV. Dose-response studies of ondansetron suggest that for maximal efficacy, prophylactic doses of 0.1 to 0.15 mg/kg up to 4 mg should be administered [47–49]. Appropriate dosing of dexamethasone is still unclear, although doses as low as 0.15 mg/kg have been effective to prevent PONV. Other maneuvers that prevent PONV are use of propofol and adequate hydration. A high dose IV fluid at 30 mL/kg was associated with less emesis than the standard 10 mL/kg therapy during strabismus repair [50, 51].

Table 32.3 Pediatric antiemetic dosing

Drug	Intravenous dose (mg/kg)	Maximum dose (mg)	Class of drug
Ondansetron	0.15	4	5HT3 antagonist
Dexamethasone	0.15 to 0.25	8	Steroids
Granisetron	0.04	3	5HT3 antagonist
Diphenhydramine	0.5	50	Antihistamine
Promethazine	0.25–0.5	25	Antihistamine

Temperature Abnormalities and Hypothermia

Children are easily susceptible to hypothermia due to limited fat reserves and a larger body surface area to mass ratio [2]. Continuous insufflation of large volumes of cold, non-humidified CO2 directly into the abdominal cavity and the use of large volumes of peritoneal irrigation pose a major risk for postoperative hypothermia in the recovery room.

A combination of active warming devices such as an infrared radiant heater, underbody warming mattress, or convective forced air warmer may be used. Warm blankets may be used to cover the head, neck, and upper torso and a towel used for a head wrap, or a heated humidifier for inspired anesthetic gases may also prevent major heat loss.

Evaporative heat loss and insensible fluid loss as well as conductive and convective heat loss are increased in this age group compared to adults. Prevention of hypothermia is crucial to avoid pharmacological and physiological consequences such as hemodynamic, respiratory, and metabolic effects, apnea, and metabolic acidosis.

Effects of hypothermia include vasoconstriction with an increase in systemic vascular resistance and central venous pressure, a decrease in renal blood flow and glomerular filtration with cold diuresis, impaired coagulation and a leftward shift of oxyhemoglobin dissociation curve, as well as an increase in wound infections and an increase in duration of hospitalization. Hypothermia may be associated with electrocardiographic abnormalities. It decreases the response to hypercapnia, increases solubility of volatile agents, increases protein binding, and reduces rate of biotransformation and clearance of medications resulting in prolonged neuromuscular blockade. Hypothermia delays emergence and discharge from the recovery room and may prolong the need for ventilatory support.

Complications of Laparoscopy

Serious laparoscopic-related complications are rare. However, it is necessary for the pediatric anesthesiologist to be aware of potential problems and possess the knowledge to diagnose and treat complications. Some problems may persist into the postoperative time frame; therefore, all patients should be carefully assessed and closely monitored at the end of anesthesia and in the recovery room.

As previously discussed, several cardiorespiratory and neurologic problems result from reduced venous return and hypercapnia secondary to pneumoperitoneum and extremes in patient positioning. During peritoneal insufflation, the diaphragm and carina are forced cephalad, while the ETT is fixed to the lip, leading to inadvertent mainstem bronchial intubation. Children are at higher risk of endobronchial migration of the ETT because of a much shorter distance between the ETT tip and the carina [7]. Cephalad diaphragm movement also causes atelectasis and shunting.

A misplaced Veress needle can lead to inadvertent CO2 insufflation into a vessel, subcutaneous tissues, preperitoneal space, viscus, omentum, mesentery, or retroperitoneum [9]. Although rare, intravascular embolization of CO2 may be lethal. It should be suspected if profound hypotension, cyanosis, dysrhythmia, or asystole occurs. Initially, there may be a sudden increase in ETCO2 concentration, followed by a decrease, owing to cardiovascular collapse and reduction of pulmonary blood flow. If gas embolization is suspected, insufflation should be discontinued and the abdomen deflated immediately. The patient should be turned left lateral decubitus with a head-down position to localize the intravascular gas into the apex of the right ventricle in attempt to prevent further embolization into the pulmonary artery. Earlier detection and confirmation of embolized CO2 may be accomplished with a precordial Doppler probe or transesophageal echocardiography. Hyperventilation with 100% oxygen for rapid CO2 elimination, aspiration of gas via a central venous catheter, and aggressive cardiopulmonary resuscitation should be implemented [52].

Subcutaneous emphysema (SE) is the direct result of insufflation of CO2 into the subcutaneous tissues and may be identified by crepitus over the chest and abdominal walls. It may be associated with increased PIPs and ETCO2 concentrations. In the event of significant CO2 absorption, SE may continue for several hours after surgery, but healthy patients are able to increase ventilation to eliminate CO2 [53]. SE is usually self-limiting and does not require any intervention unless significant hypercapnia and respiratory acidosis occur [52, 54].

Pneumothorax is a rare but potentially life-threatening complication of laparoscopic surgery, especially if not recognized and treated promptly. It can occur when insufflated gas traverses into the thorax either through a tear in the visceral peritoneum, a breach in the parietal pleura, a congenital defect in the diaphragm (patent pleuroperitoneal canal), or spontaneous rupture of preexisting emphysematous bulla. Additionally, extension of SE from the neck or face can result in gas tracking to the thorax and mediastinum, resulting in pneumothorax or pneumomediastinum. Pneumothorax should be suspected in the event of unexplained increase in PIP, hypoxemia, hypercapnia, unequal chest rise, decreased breath sounds unilaterally, or decreased TV due to reduced lung expansion on the affected side. In severe cases, such as tension pneumothorax, significant hypotension and cardiac arrest may result. The treatment is according to the severity of cardiopulmonary compromise. Minor cases may be asymptomatic requiring only conservative treatment with close observation. More severe cases require immediate release of pneumoperitoneum and intrathoracic needle decompression of the pneumothorax. If reaccumulation occurs, chest tube placement is warranted. After stabilization, conversion to an open surgery may be necessary [9, 52].

Pneumomediastinum and pneumopericardium have also been reported during laparoscopy and, although rare, can be associated with significant hemodynamic compromise. The proposed mechanisms of pneumomediastinum are similar to that of pneumothorax. Pneumopericardium occurs when insufflated CO2 is forced through the IVC into the mediastinum and pericardium or when CO2 tracks through an embryonic defect in the diaphragm that communicates between the pericardial and peritoneal cavities [55, 56]. Diagnosis is made by chest radiograph which shows

air visible in the mediastinum or pericardium. Management depends on the severity of hemodynamic compromise. Release of the pneumoperitoneum and close observation are adequate in most patients, while more severe cases may require supportive therapy, including controlled mechanical ventilation for hyperventilation to allow for CO2 reabsorption [9, 52].

Major vascular injury during laparoscopy may occur with accidental insertion of the Veress needle or trocar into major vessels such as the aorta, common iliac vessels, IVC, or hepatic artery. In the event of uncontrolled hemorrhage, immediate conversion to open laparotomy is required to control the bleeding and repair the injury. Minor vascular injuries involving the vessels of the abdominal wall (i.e., superficial and deep epigastric vessels) can also occur and usually resolve without intervention. Close observation in the postoperative period should occur as concealed bleeding owing to vascular injury can present as a fall in hematocrit values, hematoma formation, or excessive postoperative pain [52].

Conclusion

Pediatric laparoscopic surgery is growing in accordance with the rapid advancement of anesthesia and surgical techniques. Adolescence is also a time of significant change for children, even for those without significant health problems. Due to the anatomic, physiologic, and psychological differences between children and adults, the pediatric anesthesiologist caring for these patients faces a number of challenges especially during this tender age. Knowledge of pathophysiological changes, adequate monitoring, and good planning makes anesthesia for laparoscopy safe in pediatrics.

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Chapter 33
Patient Positioning for Operative Laparoscopy in Pediatric and Adolescent Gynecologic Surgery

Todd A. Ponsky, Rachel E. Hanke, Alejandra M. Casar Berazaluce, and Lesley L. Breech

Introduction

When positioning a pediatric or adolescent patient for laparoscopic surgery, a surgeon should first consider the pathology (or diagnosis) in question and the anatomy that needs to be visualized. Certain patient positions, coupled with intraoperative motion (or mobilization) of the operating table, can facilitate or complicate a surgical intervention.

If endometriosis or other reproductive system pathology is suspected preoperatively, visualization of the deep pelvis is essential for full evaluation. The ideal position will allow for perineal access with the flexibility to assess pelvic anatomy while minimizing the potential for iatrogenic injury [1]. The position most commonly used to achieve these goals is dorsal lithotomy, which can be achieved using Allen ® Stirrups (Allen Medical Systems, Acton, MA, USA) and candy cane stirrups

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Fig. 33.1 Traditional lithotomy with Allen ® Yellofin ® Stirrups provides access to perineum throughout the laparoscopic procedure

(Fig. 33.1). Allen ® Stirrups are preferred as candy cane stirrups increase the risk of peroneal and pelvic nerve compression and strain on the lumbar spine while limiting the ability to reposition the lower extremity [2].

When using either type of stirrup, first place the patient supine on the operating room table, with the buttocks at the lower break of the bed. After securing the stirrups to the frame, simultaneously elevate the legs to avoid hip joint dislocation or stress on the lumbar spine [2]. Place the feet deep into the Allen ® Stirrups, evading excess dorsiflexion and ensuring no direct pressure on the popliteal fossa (Fig. 33.2). If using Allen ® Yellofin ® Stirrups, there is no need to add additional padding along the leg [2]. Subsequently, it is important to verify symmetric knee and hip positioning, noting alignment of the knee, hip, and contralateral shoulder (Fig. 33.3) [2].

For initial perineal evaluation, high lithotomy—where the trunk to thigh angle is approximately 60 degrees—is often used. However, low lithotomy—where the trunk to thigh angle is approximately 170 degrees—is often preferred during the intra-abdominal assessment of the pelvis (Fig. 33.4) [3].

For patients with more extensive endometriosis, multiple interventions including hysteroscopy, cystoscopy, and bowel surgery may be necessary under the same anesthetic. To decrease the risk of nerve injury and lower extremity compartment

Fig. 33.2 Avoid lower extremity injury by eliminating pressure on the popliteal fossa, avoiding excess dorsiflexion of the foot, and limiting knee flexion to 90 degrees

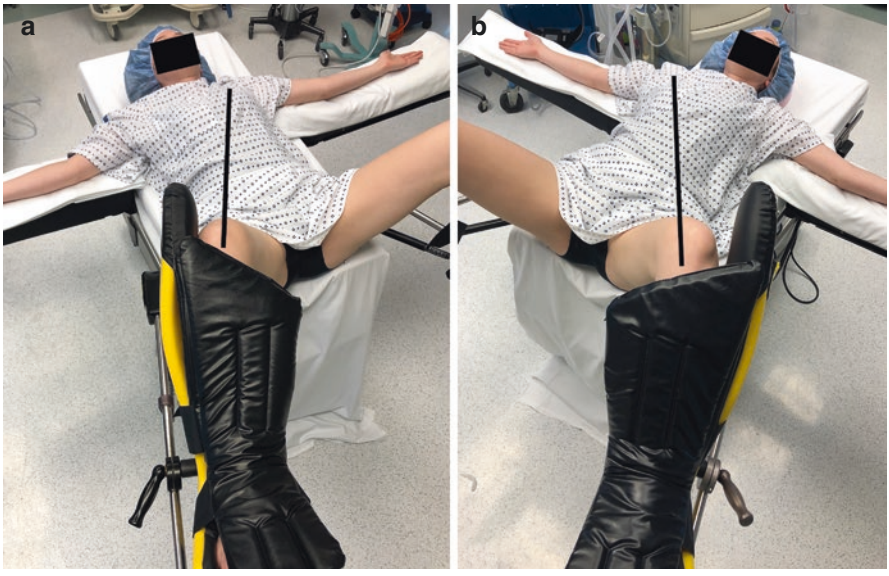

Fig. 33.3 Align the knee, hip, and contralateral shoulder to limit iatrogenic injury on the right (**a**) and left (**b**) lower extremities and pelvis

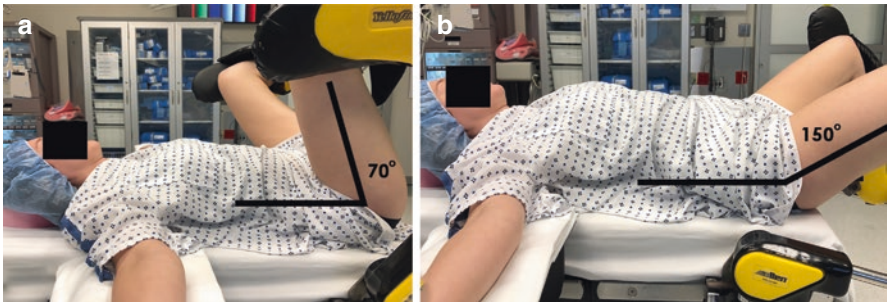

Fig. 33.4 High lithotomy (**a**) with an acute trunk to thigh angle facilitates perineal exam, while low lithotomy (**b**) with an obtuse trunk to thigh angle lowers the risk of iatrogenic injury

syndrome, it is essential to limit the use of lithotomy by transitioning to a neutral position whenever possible [3].

Patients of smaller stature or shorter leg length not suitable for pediatric stirrups can be placed in supine, frog-leg position to allow for vaginal access for examination and manipulation [2, 4].

General pediatric surgeons commonly perform diagnostic laparoscopy for suspected appendicitis or other intestinal pathologies. Endometriosis must be considered if no gastrointestinal source of pain is found. If patient is already in a supine position, the addition of steep Trendelenburg may allow for improved (but still somewhat limited) examination of pelvic anatomy (Fig. 33.5) [3]. A split leg operating table, if available, would provide flexibility to transition to a modified supine position with access to the perineum.

Strategies for Difficult Visualization

Visualization of the deep pelvis can be enhanced with some modifications. Addition of Trendelenburg positioning, with the bed placed on an incline with the patient's head below her feet, facilitates mobilization of abdominal contents cranially. This allows for improved assessment of the dependent pelvis, posterior cul-de-sac, and uterosacral ligaments (common sites for endometriotic lesions).

For improved visualization of the pouch of Douglas and the course of the ureter, it may be helpful to insert a uterine manipulator (Fig. 33.6) (Hulka-Kenwick manipulator, BD V. Mueller, Franklin Lakes, NJ, USA) which allows the surgeon to safely manipulate the position of the uterus during laparoscopy, facilitating visualization of the deep pelvis, resection of disease deep in the posterior cul-de-sac, or the use of laser therapy (Video 33.1) [3].

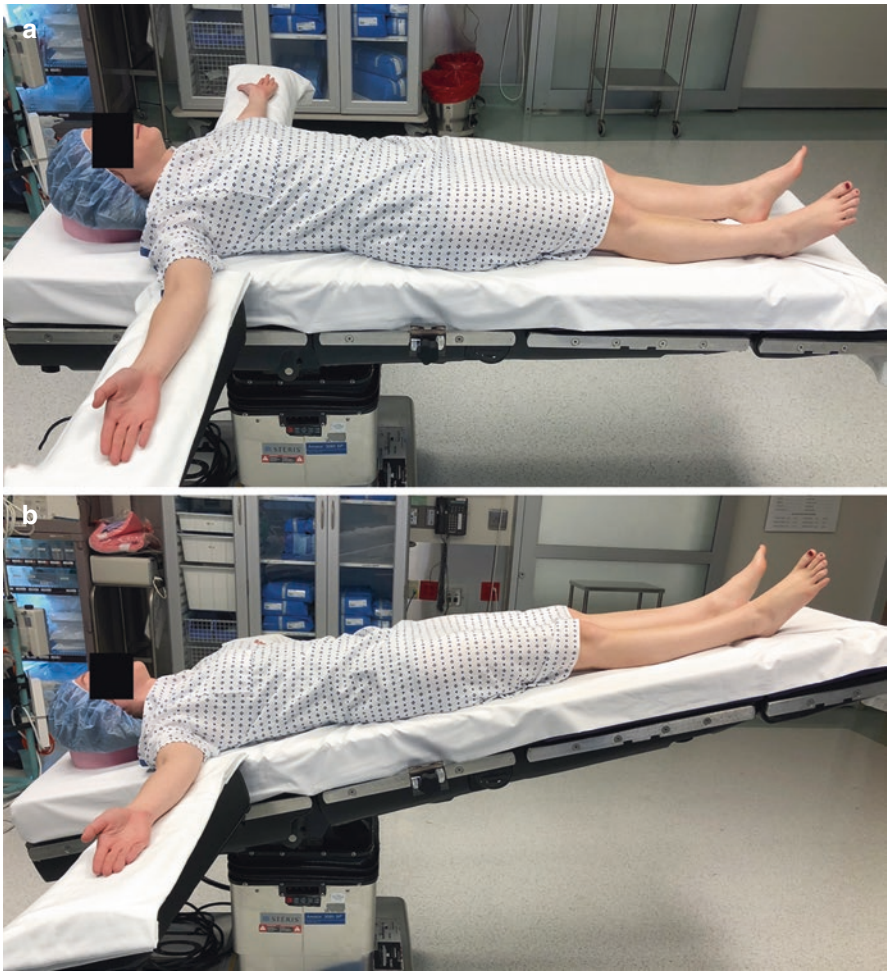

Fig. 33.5 If patient is supine (**a**) for laparoscopic evaluation, addition of Trendelenburg positioning (**b**) is helpful to manipulate abdominal contents from pelvis

Avoiding Positioning Injuries

During any surgical intervention, there is a risk of unintentional injury secondary to improper patient positioning. Although infrequent, the two most common types of injuries during gynecologic laparoscopy are nerve injuries and lower extremity compartment syndrome. Both of these complications arise from increased pressure, either directly on the nerve or by increasing compartmental pressure from fluctuations in tissue perfusion [3, 5].

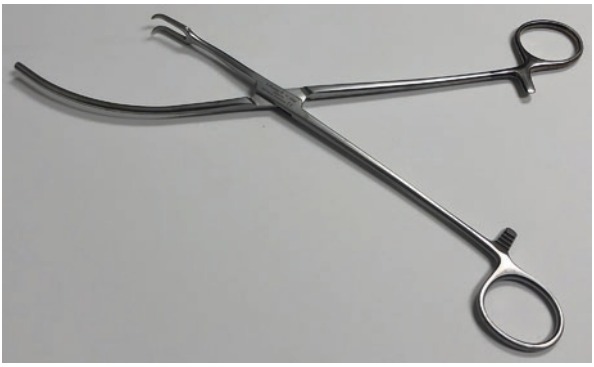

Fig. 33.6 Hulka-Kenwick uterine manipulator has hook portion to secure instrument on cervix and movable probe to mobilize the uterus

Nerve Injury

Nerve injuries related to patient positioning in gynecologic surgery are uncommon, occurring in less than 1–2% of patients. However, the pain and disability can be quite distressing [5].

Clinical presentation varies from transient numbness or tingling to complete loss of sensory or motor function. Depending on the extent of injury, patients may take days or weeks to resume baseline or partial function or permanent impairment [5].

It is important to be aware of patient characteristics which may contribute to nerve injuries; such as body mass index, either extremely high or low, can increase risk due to additional pressure from body weight or reduced natural padding of vulnerable nerves [5, 6]. Other patient characteristics to consider include malnutrition, diabetes, hypovolemia, hypotension, and electrolyte abnormalities [5].

Further precautions should be taken in long cases, especially in lithotomy, as every additional hour significantly increases risk of nerve injury. However, nerve compression can occur in as little as 15–30 minutes [5]. During each case, a conscientious surgeon should evaluate precautions taken to avoid nerve injury prior to sterile draping and throughout every operation.

Since most of these injuries are due to traction or compression of the involved nerve[s] during the operation, we will review the injury-prone areas in modified lithotomy and supine Trendelenburg positioning.

Modified Lithotomy

Modified lithotomy entails manipulation of the hip, leg, and knee—placing the femoral, obturator, sciatic, lateral femoral cutaneous, and common peroneal nerves at risk [5].

To minimize the strain on the obturator nerve, limit hip abduction to less than 90 degrees, and use low lithotomy (trunk-thigh angle at approximately 170 degrees) (Fig. 33.4). If high lithotomy is necessary for improved perineal evaluation, extend the knee 90–120 degrees, and do not decrease trunk-thigh angle below 60 degrees [5].

Femoral, obturator, sciatic, and lateral femoral cutaneous nerve strain may result from excessive hip abduction, external rotation, or prolonged flexion [5]. These movements of the hip can be increased with candy cane stirrups or additional pressure from the surgical assistant leaning on the patient's inner thigh. Avoiding any additional time in flexion, abduction, and external rotation of the hip is ideal [5].

Compression of the common peroneal nerve against the head of the fibula is the most common injury in lithotomy. This is avoided by maintaining knee flexion at greater than 90 degrees, padding the lateral aspect of the knee when using candy cane stirrups, limiting external rotation of the hip, and using boot stirrups whenever possible (Fig. 33.2) [5].

Trendelenburg Supine

Laparoscopic evaluation of a patient in supine positioning requires steep Trendelenburg to access the deep pelvis. It is essential to keep the patient safely on the bed at this angle, which can be achieved using under-patient traction pads or a shoulder brace. Placing a brace near the head or shoulders, however, may result in direct pressure on the brachial plexus, particularly if it is placed too medially or laterally [5]. If one must use Trendelenburg, it is prudent to limit the time in this position.

Risk of injury to the femoral, sciatic, and lateral femoral cutaneous nerves (as detailed above) is possible with external rotation and abduction of the hip in supine Trendelenburg positioning on a split leg bed.

Any Position

Both lithotomy and supine positioning involve manipulation of the head, shoulder, and arms—placing the brachial plexus, ulnar, and radial nerves at risk.

For patients with a small body habitus, there may be room to tuck the arms (Fig. 33.7). This should be done securely with care taken to avoid compartment compression. To prevent potential ulnar nerve damage, the arm should be pronated with additional padding along the medial epicondyle. Care should be taken to pad intravenous sites and ensure the blood pressure cuff is appropriately fitted [5, 7].

For patients with a larger body habitus, abducting and extending upper extremities to the side on arm boards may provide easier access to the surgical field. Protecting the brachial plexus involves positioning the head midline, avoiding hyperextension of the shoulder, and limiting extension of the arm to 90 degrees (Fig. 33.7) [5, 7]. It is important to supinate extended arms to avoid additional stretching of the brachial plexus or pressure on the ulnar nerve [4, 5]. Probability of injury is increased if the patient has a cervical rib or has had a previous neck or

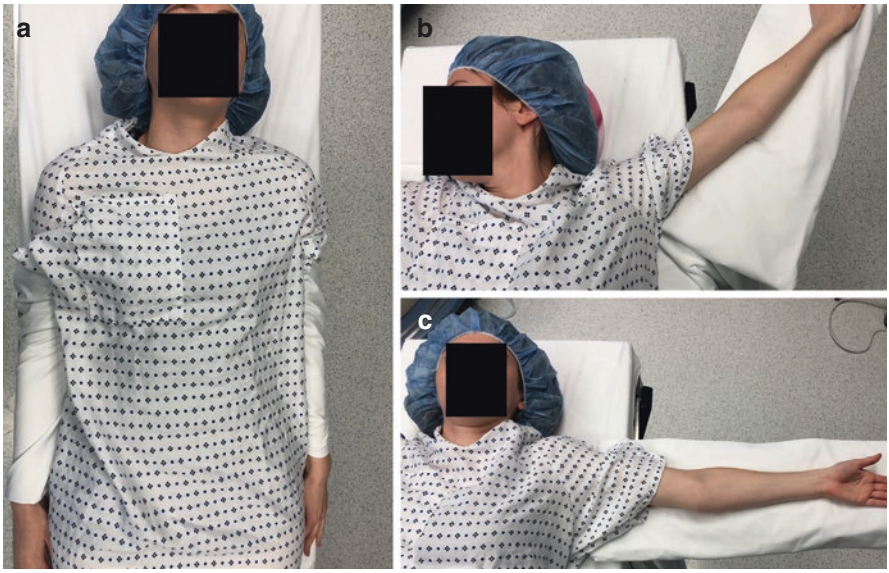

Fig. 33.7 If tucking the arms (**a**), pronate the hand and ensure appropriate padding of the medial epicondyle and IV sites. Pronating the hand, hyperextension of the arm beyond 90 degrees, rotation of the head contralaterally, and leaning the arm against side of the board (**b**) increase risk of nerve injury and (**c**) demonstrate proper positioning for extended upper extremities

shoulder surgery [5]. The radial nerve can be injured by compression against the humerus, particularly when the arm is rested at the edge of the arm board [4, 5].

Compartment Syndrome

Although development of lower extremity compartment syndrome is quite rare, and most commonly described in adults undergoing prolonged procedures, it is important to consider in all populations. The greatest risk factor is dorsal lithotomy positioning as it increases the pressure in the osteofascial compartment. This pressure is further increased in Trendelenburg positioning which decreases perfusion to the nerves resulting in neurovascular damage (Fig. 33.8) [3, 6, 8]. Other modifiable risk factors include limiting ankle dorsiflexion or use of leg holders and sequential compression devices [3, 6, 8]. Prolonged operative time (greater than 2 hours), hypotension, and epidural analgesia were also found to increase the risk of developing compartment syndrome. Optimizing each operation to decrease the probability of developing compartment syndrome should entail minimizing time in lithotomy, repositioning legs to a neutral position whenever possible, avoiding pressure on the popliteal fossa, and limiting knee flexion to 90 degrees [3]. As this complication is quite rare, it is essential to maintain a high index of suspicion in a patient demonstrating pain out of proportion to examination postoperatively [8].

Fig. 33.8 Combination of lithotomy with Trendelenburg positioning limits laparoscopic mobility externally, carries the highest risk of nerve injury and compartment syndrome, and is best avoided

Conclusion

Proper patient positioning for operative laparoscopy in pediatric and adolescent gynecological surgery is essential for successful diagnosis and treatment while decreasing operative times and optimizing surgical experience by improving visualization of the abdominopelvic anatomy. Safe positioning must be confirmed by the surgeon prior to sterile draping for every case, especially when lithotomy is utilized. Dorsal lithotomy, often providing the best perineal visualization, increases the risk of iatrogenic injury, which can be minimized by limiting time spent in this position. It is essential to consider the potential for nerve injury and compartment syndrome during every intervention.

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Chapter 34
Instrumentation for Operative Laparoscopy in Pediatric and Adolescent Gynecological Surgery

Ali Amiri and Ceana H. Nezhat

Smaller Scopes and Instruments

Recent generations of laparoscopes and instruments have been designed to offer the advantages of a smaller diameter. As such, they can provide new options for treating some patients who are smaller in size, including adolescents and pediatric patients, for a range of issues.

Minilaparoscopy utilizes a 3.5 mm diameter laparoscope, rather than the standard 5 or 10 mm diameter laparoscope, and is applicable in a wide range of procedures and approaches to surgery. Instruments range from telescopes and lightweight trocars and ports, to needle holders, a variety of graspers, as well as monopolar and bipolar instruments.

Another advantage of these smaller instruments is that they allow the use of conventional instruments to assist in manipulation when needed. With younger, smaller patients, minilaparoscopy instruments can be used with smaller incisions while offering visibility and access comparable to conventional tools. The benefits of minilaparoscopy include small incisions, improved cosmesis, reduced postoperative pain, faster recovery, and reduced risk of hernias, adhesions, and infections. Owing to the small size of these instruments, they have proven useful in a range of procedures, including diagnosis and treatment of endometriosis in adolescent patients. Additionally, performing vaginoscopy procedures on pediatric and virginal adolescent patients using the same fundamental techniques allows for a thorough examination of external and lower genital tract in an office setting or under anesthesia.

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Offering similar benefits when treating young adolescent patients, the KARL STORZ TROPHYscope®, the CAMPO compact hysteroscope, was designed for patient and physician convenience during in-office and outpatient procedures. Using a 2 mm HOPKINS® rod-lens telescope and integrated irrigation channel, the TROPHYscope® has an outer diameter of only 2.9 mm and provides enhanced light transmission. The thin outer diameter allows easy examination of the vagina, cervix, and uterine cavity without disruption of the hymen or requiring dilation of the cervix, eliminating the need for anesthesia. When the need arises, the compact device can also be used as a single-flow diagnostic hysteroscope, or as a continuous-flow operating hysteroscope through the use of an outer sheath, which increases the overall diameter to 4.4 mm.

Achieving High-Quality Visualization

Effective laparoscopic diagnosis and treatment requires a high-quality videoscope system for clear visualization of the patient's anatomy throughout the procedure and is most often based on the high-definition video camera, magnification, and transillumination system used, as well as maintaining intracavitary distension.

In some video imaging systems, the camera is a separate device that attaches to an endoscope, a "camera head." When the camera sensor is integrated into the endoscope itself, it is called a video-endoscope.

Cold light is transmitted from a light source to the telescope through a fiber-optic or liquid-crystal cable. Light transmission through a fiber-optic cable is achieved through total internal reflection. Light entering one end passes through the fiber, regardless of cable shape, constantly reflected by the fiber's inner surface, and then emerges through the other end of the cable. Liquid-crystal cables use a liquid medium and offer the capability of transmitting higher light intensity than fiber optics.

All camera heads and video-endoscopes must be connected to a camera control unit (CCU) housing the electronics and software. The CCU receives the image data from the camera and then processes and distributes it for viewing on a display or recording device.

For example, KARL STORZ currently markets a camera system based on a modular design that incorporates multiple modalities. The modular CCU consists of one CONNECT module and multiple video technology LINK modules, which can be purchased independently. At a minimum, a CONNECT and one LINK module are required for a functioning CCU. Four LINK modules are available today, of which three can be connected with the CONNECT module at the same time:

- H3-LINK® for high-definition (HD) and NIR/ICG camera heads
- X-LINK® for single-chip camera heads and video-endoscopes
- D3-LINK® for 3D HD video-endoscopes (TIPCAM®)
- 4U-LINK for 4K camera heads

The IMAGE1 S™ system enhances the visualization of HD and ultrahigh-definition (UHD/4K) images in the following ways:

- CLARA identifies and further brightens dark areas in an otherwise bright image dynamically and in real time without overexposing the bright part of the image.
- CHROMA enhances the visibility of vascularity by increasing red color contrast.
- For some surgical procedures, selecting CLARA plus CHROMA combines both enhancements to optimize viewing for those specific applications.
- NIR (near-infrared) imaging, used in conjunction with indocyanine green (ICG) fluorecence dye, enhances the visibility of blood vessels (perfusion) and biliary ducts.

In operating room (OR) settings, video display technology has also seen dramatic advances in recent years, enabling visualization of HD and 4K images. The size of video screens has also increased, with 32″ becoming the norm in modern ORs.

Extragenital endometriosis can manifest in almost any part of the body—most commonly in the gastrointestinal and urinary tracts, with cases reported in the lungs and diaphragm. Such cases require a multidisciplinary approach, which may include urologic, thoracic, bariatric, etc., surgeons present. A new technology offered by KARL STORZ that can assist a collaborative multidisciplinary team is called a "collaboratOR." This large, wall-mounted interactive display is available in sizes 55″ up to 98″ allowing multiple image display with picture-in-picture (PIP) for the team to visualize *all* relevant information. This technology allows for improved communication and coordination among the multidisciplinary team members. Remote surgical collaboration is also possible, allowing surgical teams to tap into the expertise of extended-care team members who are not present in the OR.

Several modalities are available to digitally capture surgical footage. They range from built-in capture capabilities in CCUs, to dedicated digital capture devices such as the AIDA® BELLA, to streaming technologies such as StreamConnect® that provide secure cloud-based storage as part of the electronic health record of each patient.

Maintaining Optimal Intracavitary Distension

Ideal viewing conditions for laparoscopy depend in part on keeping the cavity clear of smoke and moisture, which can cause telescope fogging. These functions are performed by the insufflator, which also helps maintain intracavitary distension during a procedure. An advanced insufflator, the ENDOFLATOR® 50, includes an integrated heating element and can operate in a sensitive mode for laparoscopic pediatric procedures. Control of insufflation pressure is optimized for younger patients, as well as for maintaining safety limits for pressure and flow. Gas heating adaptable to ambient conditions prevents fogging of the telescope and, used in combination with the S-PILOT® smoke evacuation system, provides optimal views and a stable surgical field.

Looking Forward

While pediatric and adolescent patients may represent distinctive treatment hurdles as a result of their smaller stature and youthful anatomies, the continuing evolution of medical and surgical technologies offers new alternatives for diagnosis and treatment of patients of every size and age. Solutions can be adapted to suit the challenges presented by each individual.

In coming years, images will become sharper and clearer to the surgeon's eye, while collaboration technologies will aid in the sharing of information and perspectives on new techniques and achievements. Pathologies considered difficult to identify and assess today may well become more easily diagnosed and treated as new ways of visualizing suspect tissues are introduced. In addition to more successful patient outcomes, new methods and technologies are likely to enhance key performance metrics, such as workflow and turnover rates in hospital settings, surgical time, reimbursement, and other factors.

Part XI
Interventions

Chapter 35
Surgical Interventions

Ali Akdemir, Sabahattin Anil Ari, and Fatih Sendag

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside of the uterine cavity. Such unwanted guests trigger inflammation and stimulate peripheral nerves causing pain. Symptoms may vary from minimal to severe.

Endometriotic lesions in the pelvis can be classified as superficial peritoneal, ovarian, or deeply infiltrative. The number of peritoneal regions affected by endometriosis increases during adolescence and through to one's early 20s [1]. Endometriomas occur when ectopic endometrial tissue implants in the ovary and the proceeding cyclic bleeding causes a hematoma in the ovary surrounded by ovarian cells. Deep infiltrative endometriosis (DIE) is defined as a solid endometriosis mass more than 5 mm deep in the peritoneum [2]. Surgeons are faced with DIE ordinarily in the rectovaginal septum, uterosacral ligament, rectum, rectosigmoid colon [3], and urinary tract [4].

Additionally, the exact rate of occurrence is unknown; in a retrospective cohort study of more than 9500 women undergoing laparoscopic or abdominal hysterectomy for benign indications, 15% of women were diagnosed with endometriosis [5]. The youngest endometriosis patient diagnosed in literature was 8.5 years of age [6]. Endometriosis is seen in 40% of adolescents with genital tract anomalies [7], in 50% of women with infertility [8], and in 70% of women and adolescents with pelvic pain [9].

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Clinical Manifestations

Primary dysmenorrhea begins with ovulatory cycles and is not associated with pelvic pathology. Secondary dysmenorrhea is defined as painful menses associated with pelvic pathology or a known medical condition.

Endometriosis is the most common cause of secondary dysmenorrhea; up to 70% of adult endometriosis patients state that their symptoms started before their 20s [10]. Acyclic and cyclic pain as well as bowel and urinary tract symptoms are common in adolescents with endometriosis; conversely, isolated cyclic pain is rare [9].

Vaginal examination for a young lady may cause unease. Abdominal ultrasonography or further investigations can be used instead of gynecologic examination. If endometrioma is detected, clinicians should evaluate the ureter, urinary bladder, and bowel for DIE.

Diagnosis

Secondary causes, especially endometriosis, should be considered for adolescents with cyclic or acyclic pain particularly when the patient's pain does not respond to NSAIDs or ovarian suppression as with oral contraceptives. Further investigation should be vaginal and ultrasonographic evaluation in this instance.

Endometriosis is definitively diagnosed by histological evaluation of a lesion biopsied during surgery, typically laparoscopically, and a negative histology does not rule out the diagnosis. Additionally, about 5% of these patients have Mullerian anomalies which is further discussed in Chap. 11 [11].

Endometriotic lesions in adolescents differ than those commonly seen in adults during laparoscopy. Although powder-burn lesions are common in adults, atypical red and clear lesions are more often seen in adolescents [12].

Delay in Diagnosis

NSAIDs for first-line treatments and atypical appearance of endometriotic lesions in adolescents cause delays in diagnosis. Due to the delay, endometriosis may progress to a more severe stage. Early diagnosis and interventions will contribute to a better quality of life in adolescents, as well as less damage to the ovarian tissue with less invasive ablative surgery. If possible, early diagnosis and treatment of endometriosis will stop the progression of the disease and reduce adverse long-term effects like chronic pain, endometriomas, and infertility [13].

Surgery Indications

Indications of surgery for adolescents are listed below:

- Diagnosis of medical therapy resistant persistent pelvic pain
- Medical treatment contraindications or rejection of medical treatment
- Evaluation of severe complaints that disrupt quality of life
- Exclusion of malignancy
- Treatment of anatomic abnormalities like bowel and bladder lesions

Surgery is almost always laparoscopy with the catchphrase "See and Treat." Detection of or absence of endometriosis and other adhesive pathologies is another benefit of laparoscopy. If endometriosis is detected during laparoscopy, the surgeon can utilize techniques such as lysis of adhesions, coagulation, ablation, or resection to treat. Risks of surgery include, but are not limited to, venous thromboembolism, bleeding, infection, wound infection, adhesion formation, and injury to surrounding structures. Some families may choose empirical hormonal treatment with suspicion of endometriosis without definitive diagnosis to avoid the risks associated with surgery. Regardless, the adolescent patient, her family, and her physician should discuss all possible means of management before settling on a treatment plan.

Techniques of Diagnostic Laparoscopy for Adolescent Endometriosis

When entering the abdomen of an adolescent, keep in mind the smaller stature and distances to vital organs compared to adult woman. The gynecologist is closer to the great vessels than ever before! A systematic approach will facilitate an uncomplicated access to the pelvis. Following the same steps in every operation will make the surgery safe and fast. Systematic evaluation should include upper abdomen, uterus and adnexa, the peritoneum of ovarian fossae, vesicouterine fold, Douglas and pararectal spaces, the rectum and sigmoid, as well as the appendix and cecum. The ureters, bowel, and bladder should also be evaluated for endometriosis [14].

Endometriotic lesions may present as transparent-clear, yellow-red, or red-black. Blue-black lesions or "powder burns" are typical. In adolescents, transparent, vesicular, or red flame lesions are more common. These lesions are metabolically active, have greater prostaglandin levels than an adult's lesions, and cause more pain [15]. The accuracy of diagnosis depends on the type of lesion, location, severity of disease, and the experience of the surgeon [16]. Filho et al. reported that laparoscopic findings had 72% positive predictive value, 98% negative predictive value, as well as 79% specificity and 98% sensitivity compared with pathological evaluation [17]. When pathology results are negative but endometriosis is present on laparoscopy,

the patient should still receive endometriosis treatment because this error could be due to inadequate sampling.

Due to the difficulties in diagnosis, several approaches have been defined for the recognition of lesions. One technique utilizes a laparoscopic camera from several millimeters to screen the peritoneum, while another fills the pelvis with saline before inspecting via an optic device [18].

Ideally, biopsies should be taken at the start of surgery followed by the excision or ablation of all suspected endometriotic lesions. Note that if biopsy is not taken at the beginning, ablation of all endometriotic lesions can deprive the clinician from pathological diagnosis. Furthermore, laparoscopic diagnosis is not confirmed by pathological reports but is sufficient for medical treatment of endometriosis after operation. Peritoneal striping is not recommended due to serious concerns such as adhesion, infertility, and intestinal complications, and the short- and long-term results of this method are insufficient [19].

While many young patients diagnosed and treated laparoscopically have American Society for Reproductive Medicine stage I or II endometriosis, studies have reported cases of stage III and IV as well as deep infiltrative endometriosis [21–23]. It should be emphasized that the complaints are independent of the stage when informing the family and patient before and after the operation [20]. Nezhat and colleagues reported that in their laparoscopically diagnosed adolescent endometriosis series, 68% had stage I, 20% had stage II, and 12% had stage III. There were no stage IV patients [21]. Matalliotakis et al. in their cohort found 45.4%, 36.4%, 14.5%, and 3.7% with stage I, II, III, and IV endometriosis, respectively [22]. Audebert et al. in 2015 recorded distribution of stages as follows: 60% stage I-II, 40% stage III-IV, and 10.9% defined as deep infiltrating endometriosis [23].

Treatment

The American Society for Reproductive Medicine (ASRM) Practice Committee affirms that “endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures” [24]. Treatment of endometriosis should be individualized, and presentation (pain, infertility, mass in the abdomen), disease severity, localization of the disease, desire for fertility, age of the patient, and possible complications should be considered. Analgesics, hormonal treatment, and surgery are available options for treatment and should be combined. Symptomatic analgesics, conservative surgery, and suppressive hormonal treatment after intervention are recommended management instruments [19].

In patients presenting with primary dysmenorrhea, if symptoms disrupt school or social life, medical treatment for 3–6 months should be considered before surgery. For medical treatment, NSAIDs and low-dose estrogen/progestin oral contraceptives or progestin only are good options. Before starting treatment, the patient and

her family should be educated about treatment without definitive diagnosis and the possible side effects. A comprehensive overview of medical treatment is available in Chap. 39. Surgery should be considered for patients who are not responding to empirical treatment for 6 months or who do not want to start treatment without a definitive diagnosis.

Preoperative Preparation

Adolescents and their parents should be informed about the purpose, benefits, possible risks of surgery, and the alternative treatment options available. Written informed consent must be obtained. It should also be emphasized that endometriosis is a chronic disease that can recur and that the patient should undergo routine surveillance and possible additional surgery if recurrence occurs.

The severity of endometriosis symptoms and the stage of disease are not related. Surgery may be considered before simple interventions. To minimize complications with surgery, preoperative mechanical or medical thromboprophylaxis should be considered.

Some surgeons prefer antibiotic prophylaxis especially should a vaginal or intestinal procedure also be planned [19].

Positioning is same as for adult patients and has been comprehensively discussed in Chap. 33. If the adolescent is tall enough, an Allen stirrup can be used; for shorter patients, a frog-leg position may be preferred. The nasogastric and orogastric catheter should be inserted before entering the abdomen. A Foley catheter may be employed to provide bladder decompression during the operation and will also help fill the bladder with saline and assist to determine the cleavage line for possible bladder involvement.

Surgical Treatment

Diagnosis and treatment for endometriosis are intertwined, and the gold standard for both is laparoscopy. For a young lady who does not respond to empirical treatment for 3 or 6 months and experiences disadvantages due to pain in her school or social life, definitive diagnosis and treatment should be considered. Endometriosis has been detected in 70% of patients who were unresponsive to NSAIDs and hormonal treatment [9].

Although open surgery has been used historically for endometriosis, in essence, it has been replaced by laparoscopy. Effectiveness of the two approaches on pain is equal [14]. Less postoperative pain, shorter hospital stays, shorter recovery, and better cosmetic outcomes are the obvious benefits of laparoscopy. Additional advantages of laparoscopy included the magnifying effect of the camera and facilitated

dissection via carbon dioxide [25]. Nowadays, laparoscopy is widely used independent of the stage of the disease.

Staging of disease is determined by performing an orderly sequence of pelvis assessment at the beginning of the operation. Normal anatomy is then restored by removing adhesions followed by excision or ablation of the lesions.

- *Ablation*: Eliminating endometriotic lesions via electrosurgical or ultrasonic coagulation or laser vaporization (Fig. 35.1)
- *Excision*: Removing lesions by cold scissors (Fig. 35.2)

Coagulating all lesions will deprive the patient from definitive pathological diagnosis. Possible thermal damage to other pelvic organs during ablation should also be considered. At Ege University Hospital, we prefer excision of lesions instead of ablation.

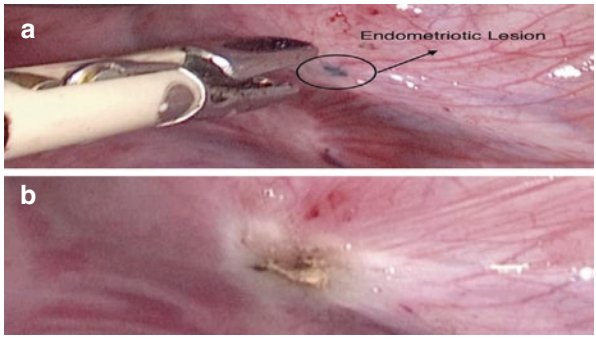

Fig. 35.1 Ablation of endometriotic lesion. (**a**) Ablation with bipolar instrument. (**b**) Ablated lesion

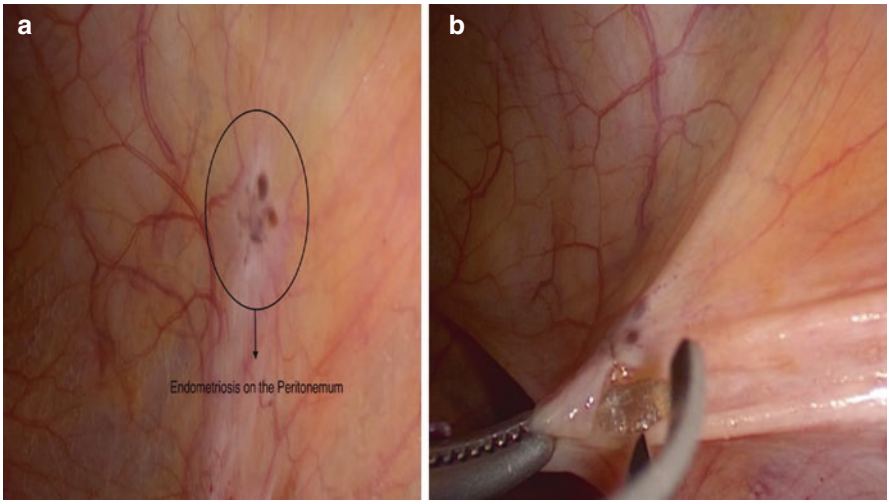

Fig. 35.2 Excision of endometriotic lesion. (**a**) Lesion of endometriosis on the peritoneum. (**b**) Excision of lesion via cold scissors

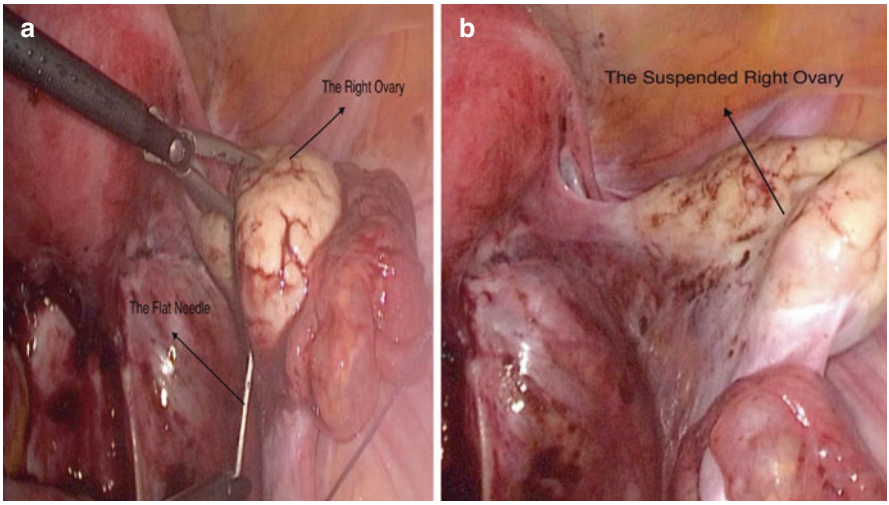

Fig. 35.3 Suspension of the ovary. (**a**) Passing of the flat needle. (**b**) The suspended ovary

Resection of Infiltrative Endometriosis

If deep infiltrative endometriosis is determined during dissection, nodules should be removed with maximum care to avoid injury to adjacent organs. These nodules are the origins of pain rather than endometriomas. The surgeon should investigate further the uterosacral ligament, rectovaginal septum, bladder, and rectum for additional nodules of deep infiltrative endometriosis. Before starting surgery for deep infiltrative endometriosis, the surgeon may choose to suspend the ovaries to the abdominal wall with temporary sutures to avoid potential injury (Fig. 35.3). Unless the vaginal route allows for the use and placement of a uterine manipulator, the uterus can be suspended to the abdominal wall as well. Subsequently, if the ureter is thought to be involved, it should be dissected by finding in pelvic brim. Uterosacral ligament and rectovaginal septum with endometriotic nodules or other peritoneal deep infiltrative lesions ought to be excised via cold or ultrasonic scissors.

The retroperitoneal dissection is carried out starting at the pelvic brim just medial to the infundibulopelvic ligament. Once the peritoneum is incised, the carbon dioxide starts to enter the retroperitoneal space and facilitates dissection. After identifying the ureter, dissection proceeds through the uterosacral ligament junction to the uterus. During this dissection, maximum care is taken to avoid injury to the ureter. Ultrasonic scalpel or conventional bipolar or monopolar instruments can be used. Our preference is the ultrasonic scalpel; preference is for use of a harmonic scalpel. Note that the active blade should be kept away from the ureter. While performing the ureterolysis, the ureter is lateralized (Fig. 35.4). Next incise the space between the uterosacral ligament and rectosigmoid colon. It is important that the surgeon remembers that the fatty tissue belongs to the rectum which explains why the dissection avoids this fatty tissue and follows a cranial to caudal direction lateral to the

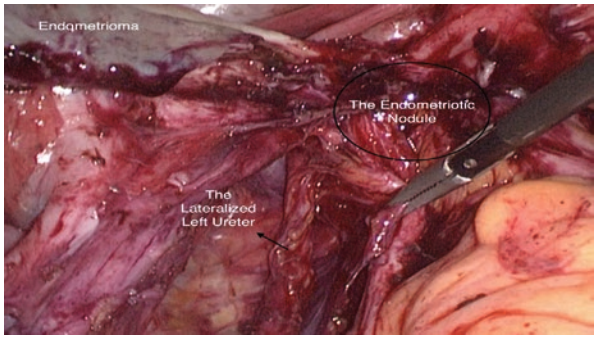

Fig. 35.4 Lateralization of the ureter

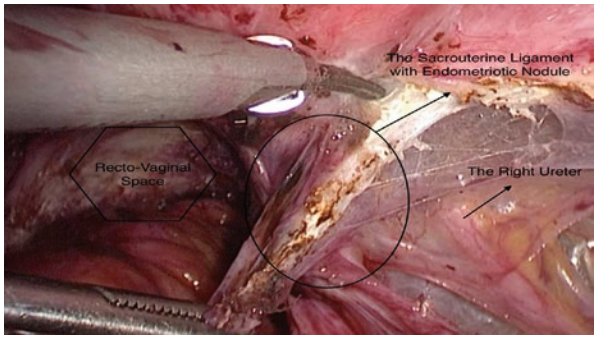

Fig. 35.5 Excision of deep infiltrating nodule

rectum to develop the rectovaginal space laterally. If performing this dissection between the rectum and uterus, great care should be taken to find the correct dissection plan. The underlying reason for this increased vigilance warming is the endometriotic nodule itself. Dissection of the rectovaginal space laterally, to the rectum on both sides, and proceeding with dissection caudally allows clean dissection beyond the rectovaginal nodule caudally. The rectum can then be separated from the vagina in a caudal to cranial direction more safely, and the rectum can be displaced posteriorly while the nodule is left attached to the uterus and vagina anteriorly and excised safely without causing any injury to the adjacent organs (Fig. 35.5). During excision of the nodule, posterior colpotomy has to be performed especially with larger nodules attached to the vagina. In cases of posterior colpotomy, the surgeon should take precautions to maintain the pneumoperitoneum by addressing any vaginal gas leakage. Our routine is to close the vagina with a surgical glove filled with gauze sponge. Colpotomy can be closed laparoscopically or vaginally after removal of all the specimens through colpotomy incision vaginally. In case of the existence of endometriotic lesions on the rectum, surgical options include shaving, discoid, or segmental resection.

Treatment of bladder lesions involves the removal of the nodules and the primary repair of the defect. If the ureter lesion is considered or there is full-thickness involvement, the ureter should be catheterized, excision of nodules or segmental removal performed, and end-to-end anastomosis conducted.

Early stages of disease are more common for adolescents, and bowel involvement is rare. Superficial shaving, discoid, or segmental resections are techniques for bowel endometriosis. When rectal surgery is necessary, intra- and postoperative complication rates have been reported as 2.1% and 13.9%, respectively, by Kondo et al. [26]. Patient's age and symptoms must be reviewed several times before making radical decisions for treatment of the ureter, bladder, or intestinal involvement.

Ovarian Cystectomy

Removal of endometriomas over 3 cm is superior to drainage or coagulation in terms of recurrence [14]. An incision can be made into the cyst on the opposite side of the hilum of the ovary, and a cleavage line should be identified. The cyst is excised by applying traction and countertraction to the ovarian tissue and cyst wall. Both sides, particularly the ovarian tissue, should be grasped gently (Fig. 35.6). After extirpation of cyst wall, hemostatic sutures are preferred to coagulation. In a high-quality randomized controlled trial, Sahin and colleagues showed hemostatic sutures to be superior to bipolar electrocoagulation for hemostasis after cystectomy for ovarian reserve. Ninety patients participated in the trial, and anti-Mullerian hormone levels in the suture group did not change pre- or postoperatively, whereas a statistically significant decrease was seen in the bipolar electrocoagulation group [27]. After hemostasis, the cyst wall may be removed from the abdomen via endo-pouch.

Combined techniques for endometrioma surgery should be considered if concern for decreased ovarian reserve is present [28]. This approach removes the

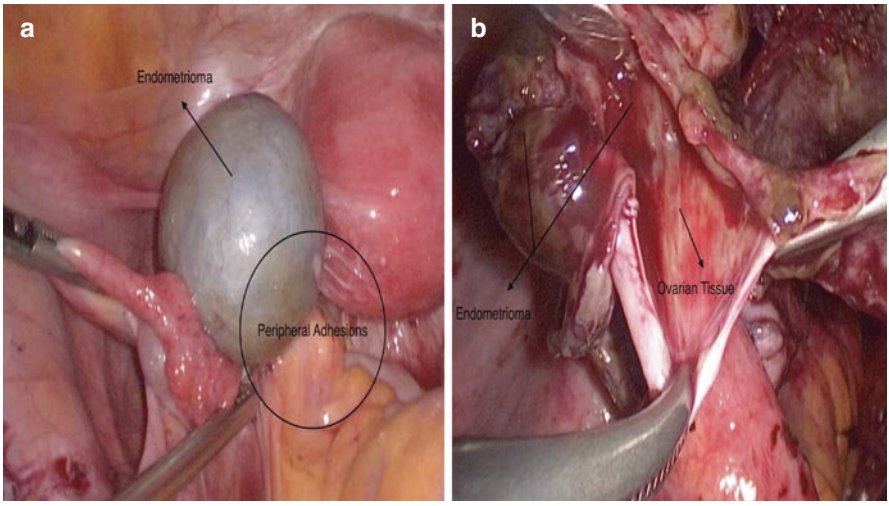

Fig. 35.6 Ovarian cystectomy. (**a**) Endometrioma. (**b**) Stripping of cyst wall

endometriotic cyst from the ovary without removing the segment of cyst wall attached to the ovarian hilum. The cyst wall attached to the ovarian hilum is electrocauterized or vaporized by CO_2 laser. By doing the surgery this way, the risk of bleeding from the ovarian hilum and the risk of applying excessive electrosurgery to stop the bleeding are eliminated, and the likelihood of jeopardizing ovarian reserve is diminished. Muzii et al. compared two techniques, conventional stripping and the combined approach, in terms of *recurrence* and *ovarian reserve* in a multicenter randomized controlled study and found there to be no difference between the two outcomes [29].

Endometriosis ought to be staged at the time of surgery; this aids follow-up and determining if additional surgical intervention is indicated. Of course, it is best to video record the laparoscopic findings for medical, scientific, and documentation purposes.

Prevention of Adhesions

Intraperitoneal adhesions can cause pelvic pain, subfertility, dyspareunia, and bowel obstruction. Moreover, this adverse condition(s) will incur further financial burdens. Oxidized regenerated cellulose can be a prevention technique for adhesions after surgery, although its true effectiveness is not certain [14]. Gel agents such as carboxymethylcellulose and polyethylene oxide, hyaluronic acid-based gels, polyethylene glycol gels, 0.5% ferric hyaluronate gels, and sodium hyaluronate spray are all available mediums for preventing adhesions, although the safety and effectiveness of these products is unclear due to lack of evidence. Furthermore, ovarian suspension for 36 hours to 7 days has been hypothesized for adhesion prevention [30]. In a systematic review of eight articles investigating the efficacy of ovarian suspension in preventing postoperative ovarian adhesion formation in women undergoing laparoscopic surgery for stage III-IV endometriosis, researchers concluded this approach to be safe, simple, feasible, and effective [30].

Complications

Complication rates are generally the same as for other laparoscopic procedures. In a large study of 30,000 laparoscopic surgeries for gynecology, proximate organ injury was found to be the most commonly occurring complication with complication rates during endometriosis-related procedures at 0.1% and 3.6% for deep infiltrative endometriosis [31].

Pain Reduction

Many women have reported a decrease in their endometriosis-associated pain following surgery. A 2014 systematic review showed that women who had undergone operative laparoscopy described improved pain relief within 12 months, three times more than those who underwent diagnostic laparoscopy [32]. Surgical treatment will reduce pain; however, approximately 20% of patients will undergo another operation within 2 years due to recurrent symptoms [33]. In a 10-year follow-up, recurrence rates reached 40% [34]. Advanced disease seems to be associated more with recurrence due to lack of complete resolutions in the first surgery. Parazzini et al. published that women with stage III-IV disease had higher recurrence rates than women with stage I-II within 2 years (14% and 6%, respectively) [35].

Postoperative Management

According to literature, if endometriosis is eliminated via surgery in adolescents and compounded with proper medical treatment, the complaint of pain decreases and disease progression is halted [13, 36, 37]. Postoperative hormonal therapy should continue until the patient desires fertility. Combined low-dose oral contraceptives, progestin-only pills, and intrauterine devices with levonorgestrel are all options for suppression. Contrariwise, narcotic analgesics are not suitable for this patient group [19].

Adolescents with endometriosis should be evaluated regularly, and their pain should be questioned. It ought to be explained to the patients in an appropriate way that they may not experience a completely painless period. Support groups for adolescents with endometriosis are available and can be very beneficial (www.youngwomenshealth.org, www.endometriosisassn.org, www.endofound.org).

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Chapter 36
Laparoscopic Surgery in Adolescent Endometriosis

David Soriano and Yochay Bar-Shavit

Recognition of endometriosis (EM) in adolescents has increased in recent years. The clinician should be aware of unique aspects of this population, and some of these relate to surgical intervention. The purpose of this chapter is to present updated information and the accumulated evidence on surgery in adolescent EM and to discuss surgical indications, findings, outcomes, and specific aspects of the disease that relate to surgery. The gold standard for EM diagnosis is analysis of direct tissue biopsy [1], which is taken during laparoscopic surgery. Accordingly, most of the data on this subject originate from case series of patients with surgically confirmed diagnoses [2]. This evidently determines the characteristics of the patients who are considered to have EM, who may not represent the entire population of affected persons.

EM may be an underdiagnosed condition in general; the diagnosis in adolescents is particularly challenging. This could be attributed to a number of factors discussed in detail below.

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Patient Presentation

The vast majority of adolescent patients present with pain; the leading symptoms are dysmenorrhea and pelvic pain [3, 4]. In adolescent EM, the clinical presentation is different from that in adults. Adolescents with EM are more likely to describe noncyclical pain, in contrast to adults with EM, who present classically with complaints of cyclical pain. Notably, adolescents with endometrioma tend to have a predominant symptom of pain, while a coincidental finding of an endometrioma is much more likely among adults [5]. Dyspareunia may be reported among those sexually active [4, 6]. Complaints of infertility rarely present among adolescents, although surprisingly Audebert et al. [7] reported that 9% in their series (aged 12–19 years) had a history of infertility.

Presenting symptoms that are commonly reported in adolescents with EM can be misleading to physicians unaware of their relevance; these include fatigue, bladder complaints, exercise pain, and gastrointestinal complaints such as dyschezia, constipation, and diarrhea. The differential diagnosis for chronic pelvic pain (CPP) is wide [8]; however, pain that is unresponsive to medical therapy raises a high suspicion of EM. A meta-analysis of 15 studies published during 1980–2011, of 880 young females with CPP or dysmenorrhea, and laparoscopically confirmed EM [9], reported an overall prevalence of visually confirmed EM of 62% among all adolescents who underwent laparoscopic investigation for pain, 49% in adolescents with CPP not necessarily resistant to medical therapy, 75% in those for whom CPP was resistant to medical therapy, and 70% in adolescents with dysmenorrhea. Another sign for high suspicion is severe dysmenorrhea that interferes with other activities of daily living, as EM was found in 73% and 67% among such adolescents in Reese et al. and Laufer et al.'s reports, respectively [4, 10].

An adolescent presenting with the symptoms mentioned above, together with a family history of EM, should raise a very high index of suspicion for EM. Family history seems to be the most salient risk factor in clinical practice. In monozygotic twins, a high concordance rate was reported for histologically proven EM and even for the EM stage [11]. A first-degree relative with EM confers a *sixfold increase* in the risk for EM, but any other family member with EM is also a risk factor. In the reports by Dun et al. and Audebert [7, 12], 56% and 34% of patients, respectively, had a positive family history of EM. Case series consistently report a first-degree relative with EM in about 25–30% of the patients [7, 13]. An increased risk of early age EM is found in Mullerian anomalies with obstruction (further discussed together with surgical management in the section on "Surgical Principles," later in this chapter). Some authors identified menarche prior to age 14 as a significant risk factor [14, 15]. Failure of medical treatment for symptomatic alleviation (or noncompliance), especially in the context of severe interference in daily living activities, and when accompanied with known risk factors, is an indication for laparoscopic

intervention to treat pain. Significant pain relief was shown in adult patients who underwent excision and adhesiolysis compared to diagnostic laparoscopy [16].

The *time to diagnosis from symptom onset* is a major concern of EM. This time lapse is accompanied by years of discomfort, pain, and distress and can have adverse psychological effects [12, 17]. Adolescents have been reported to be evaluated by an average of three physicians [12], including psychiatrists and orthopedic surgeons, before EM is diagnosed. This highlights the need for early diagnosis of EM in adolescents with dysmenorrhea and CPP. Delay in EM diagnosis may be attributed to lack of awareness among patients and their families, as well as among physicians. Main contributing factors to such are the diversity of symptoms, the overlap with benign conditions, a low index of suspicion, cultural attitudes, normalizing painful menstruation, and concern regarding surgical intervention [1, 18].

The upshot is that *a primary indication for laparoscopic surgery should be diagnosis*, as this is the gold standard for diagnosing or ruling out pelvic EM. Despite extensive studies on various biomarkers, no single entity or panel has yet been validated with sufficient sensitivity and specificity to diagnose EM. Although pelvic imaging techniques (ultrasound, MRI) can assist in identifying structural causes of pelvic pain and individual lesions, a normal imaging exam does not rule out EM.

Surgical Findings

Laparoscopy to date offers a low morbidity gold standard diagnostic tool for identifying EM, while all other noninvasive techniques are inferior [19–23]. However, among the limitations of laparoscopy for EM diagnosis is false negativity. This can be due to subtle lesions that may be masked by hormonal treatment [24] or failure of the operator to recognize the distinctive features of lesions in adolescents with EM, which are somewhat different from those usually seen in adults (Figs. 36.1,

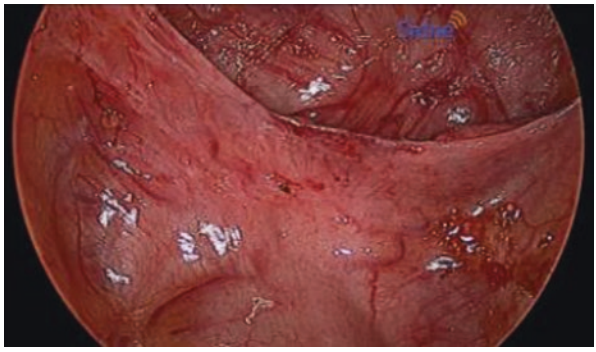

Fig. 36.1 Red/flame-like lesions of endometriosis in the adolescent. (From Stuparich MA et al. [8])

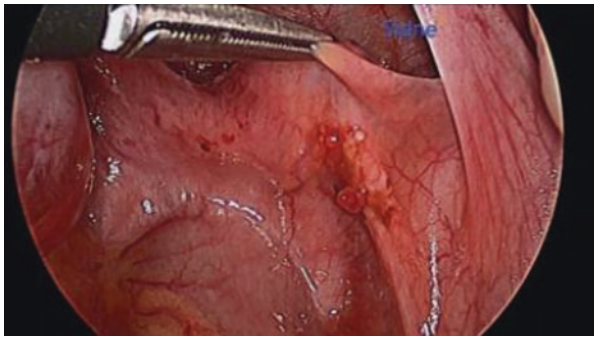

Fig. 36.2 Clear/polypoid and vesicular lesions of endometriosis in the adolescent. (From Stuparich MA et al. [8])

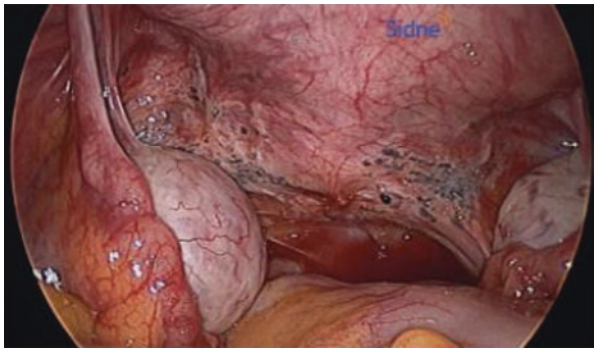

Fig. 36.3 "Powder-burn" lesions of endometriosis, more commonly seen in the adult. (From Stuparich MA et al. [8])

36.2, and 36.3) [8]. For example, in adolescents, lesions tend to have more of a "powder-like" pattern (black with a white scar). In Dun et al.'s series [12], the lesions were mostly peritoneal defects, atypical white/fibrotic lesions, clear lesions, ovarian or cortical, hemosiderin/pigmented, and hemorrhagic. False-positive diagnosis can stem from findings visually attributed to EM without histological sampling. Thus, we support the recording of videos and images and frequent performance of biopsies.

Early reports suggested that EM in adolescents is almost always early stage (revised American Society for Reproductive Medicine Stage (rASRM) Classification [25] stage I and II). Accordingly, in Laufer et al.'s series [4] (1997), all 39 patients under age 22 years and with refractory CPP had early stage EM (stage 1–2), as did over 90% of 49 adolescents in Reese's case series [10] (1996).

A trend toward a greater proportion of advanced disease was reported in a number of more recent publications [26, 27] (Table 36.1). A meta-analysis of studies published during 1980–2011 reported that in eight of 15 studies that included the rASRM staging system, the distribution of EM staging was 32% for moderate and severe EM. Advanced stage EM was reported by Stavroulis et al. [28] (2006) as 54.5%, by Davis et al. [29] (1993) as 50%, by Vicino et al. [30] (2010) as 69%, by Yang et al. [3] (2012) as 89%, by Smorgick et al. [31] (2014) as 23%, and by Audebert et al. [7] (2015) as 40%. The distribution by type of the most severe

Table 36.1 Staging of EM in adolescents according to rASRM

	Age range	Cases (*n*)	GTA (%)	I (%)	II (%)	II I(%)	IV (%)	Ovarian endometrioma (%)
Vercellini et al (1987)	10–19	18	NM	67	33	0	0	NM
Davis et al (1993) [29]	13–20	36	0	50[a]		50[b]		19
Reese et al. (1996) [10]	11–19	49	NM	80	12	6	2	NM
Laufer et al (1997) [4]	13–21	31	0	77	23	0	0	0
Bai et al (2002) [69]	14–21	39	NM	10	44	28	18	NM
Ventolini et al (2005) [59]	12–18	52	0	14	39	43	4	0
Stavroulis et al (2006) [28]	13–20	11	0	45[a]		55[b]		0
Vicino et al (2010) [30]	15–21	38	0	18	13	34	34	3
Roman (2010) [13]	14–20	20	NM	40	45	5	10	NM
Yang et al. (2012) [3]	12–20	63[c]	24	8	3	52	37	87
Smorgick et al (2014) [31]	<22[d]	86	0	67	9	8	15	16
Dun et al (2015) [12]	<21	25	NM	68	20	12	0	0
Audebert et al. (2015) [7]	12–19	55	4	60[a]		40[b]		33

From Benagiano et al. [26]
Adapted and completed from Brosens et al. [18]
GTA genital tract anomaly, *NM* not mentioned
[a]Stages I and II
[b]Stages III and IV
[c]Of all the 15 cases with anomalies, ovaries were involved in 14 (93%), whereas rectivaginal pouch and uterosacral ligaments were only involved in two cases (13%). Of the 48 cases without anomalies, however, 26 had rectivaginal pouch or uterotacral ligaments involved (26/78)
[d]Age of revised-American Fertility Society group I and II versus III and IV, respectively: 18.7 ± 2.2 years and 20.4 ± 1.4 ($P < 0\ 001$)

lesions reported by Audebert et al. was 56% superficial peritoneum, 33% ovarian EM, and 11% deep infiltrating EM (DIE) (Fig. 36.4). Endometrioma was reported in Audebert et al. as 42% and by Smorgick et al. as 16% (71% left-sided, 14% right-sided, and 14% bilateral).

The increasing proportion of more advanced findings observed in recent years could raise concern. It could reflect a true change that has occurred in the disease pattern over time. For example, the consequences of declining menarche age and lifestyle changes on EM disease are unknown.

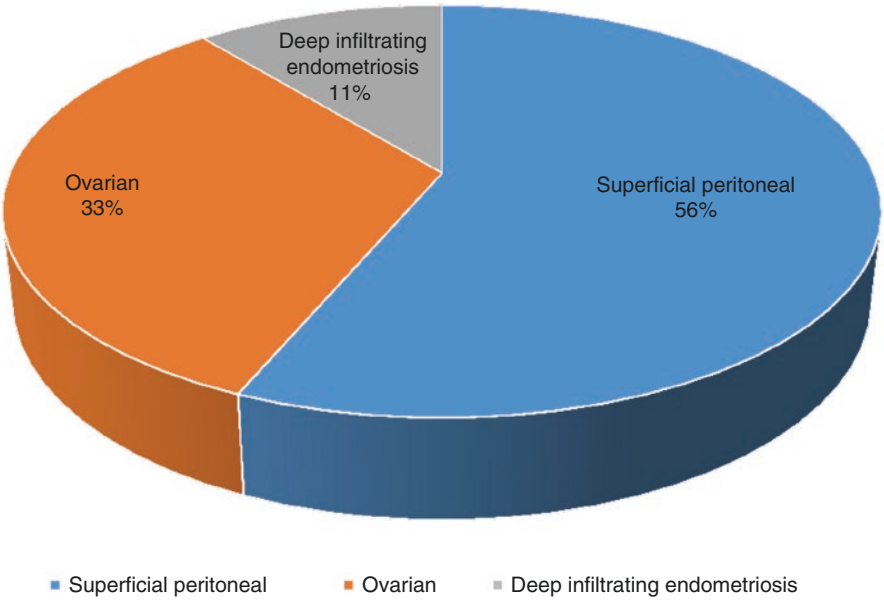

Fig. 36.4 Distribution of type of endometriosis by most severe finding

Of particular concern is the finding of ovarian endometrioma in adolescents (this was thought to be rare but is presently a more common finding), due to the potential negative impact on fertility and ovarian reserve. Debate is ongoing regarding the best treatment modality for endometrioma, especially in the adolescent population, in which ovarian reserve and fertility preservation is highly valued.

Evidence shows that advancing inner cortex fibrosis and devascularization can progressively reduce follicle reserve [32]. Histologic findings showed that small type endometriomas (type 1) are limited in size by scarring and fibrosis and that large endometriomas (type 2) develop by colonization of endometriotic cells on functional cysts [33]. The minimal cutoff diameter of endometrioma for surgical intervention of 3 cm, as recommended by the European Society of Human Reproduction and Embryology (ESHRE) guidelines [1], has been questioned, since the condition rarely entails a sole lesion or sole source of pain [34], and the damaging effects of the ovarian endometrioma itself on the follicle concentration and fibrosis of the ovary were observed in endometriomas smaller than 4 cm diameter [32]. Disruption and disorganization of the cortical wall result in loss of a cleavage plane and create a surgical challenge. Early intervention seems to have twofold importance in the context of endometrioma: for one, to halt the negative impact of the endometrioma on the follicular reserve; and for another, to reduce surgical damage to the follicular reserve [35]; however, no randomized controlled trials (RCTs) support the benefit of early intervention.

Surgical Principles

Prior to EM surgery in adolescents, a workup is recommended to assess the extent and involvement of the disease and to weigh the risks, benefit, and extent of the surgery planned.

Upon entry, extra caution should be taken due to the smaller size of adolescents. Measures to be considered are a higher entry pressure of 20 mmHg, sight of entry port, and the use of a 5 mm port.

A systematic examination of the abdominal compartment and pelvis should be carried out, including the peritoneum of the diaphragm, the side walls, and the anterior and posterior compartments of the pelvis and adnexa. We encourage recording images, as these are important in case of future repeat surgeries and follow-up. We are in favor of taking biopsies since histology confirmation is the gold standard, and lesions among adolescents are often subtle, as mentioned above (in adults, the recommended good practice point in the ESHRE [1]). The EM lesions can be either ablated or removed. Ablation and excision techniques for peritoneal EM reduce pain [36]. Despite the lack of high-level evidence, we advise excision of peritoneal EM rather than ablation, to reduce recurrence. In the advanced form of EM, excision of the lesion is recommended, in accordance with the ESHRE guidelines (level A, B) [1].

Endometrioma was described above as requiring particular surgical considerations. Data comparing surgical techniques for treatment of endometrioma are available for adults, but not for adolescents. As mentioned, endometria is usually accompanied by lesions in the bowel and urinary system, and this should be considered in the surgical planning [34, 37]. Saridogan et al. formulated recommendations for the surgical treatment of endometrioma [38]. Following a systematic inspection, peritoneal washings and biopsies should be obtained if suspicious findings are apparent; otherwise, this is not routinely recommended. The endometrioma should be separated cautiously from the side wall, to which it is usually adherent, as the ureter may be involved in cases of dense adhesions (this would be an indication to start dissecting the ureter proximally in an area of healthy tissue). Endometrioma drainage generally results. The rupture site of the cyst should be extended, and the cyst cavity irrigated and inspected; care should be taken to remain in safe distance from the hilum. Three main techniques have been described for surgical treatment of endometrioma – cystectomy by the stripping technique, ablation by laser or plasma energy, and electrocoagulation. *Cystectomy* includes finding the cleavage plane, which may be challenging as mentioned above. The use of cold cut (with caution from areas of blood vessels, to avoid use of hemostatic energy detrimental to the ovarian reserve) may facilitate finding the plane. Diluted synthetic vasopressin solution may be injected under the cyst capsule, thus dissecting the plane and also reducing bleeding during cystectomy. Careful plane identification, gentle traction, and countertraction, with precise spot bipolar coagulation when needed, are key to minimizing ovarian reserve damage and full resection of the endometrioma. Following capsule removal, hemostasis should be confirmed, while avoiding the hilum – preferably using sealants or suturing rather than bipolar coagulation. Ovary reconstruction by suturing

should be considered for large endometriomas, ideally placed in the ovary to avoid adhesion formation. In cases of dense adhesions or lack of a cleavage plane, it is advised to consider a small biopsy and the use of ablation techniques. *Ablation* includes fenestration and washing of the endometrioma, followed by destruction of the cyst wall with an energy source [39]. *Laser ablation* is done by using the laser beam to ablate the entire inner surface of the cyst wall. Endometriotic tissue is only superficial, so the aim is to vaporize the endometriotic cyst lining only until pigmented tissue is no longer seen. Intermittent irrigation is encouraged to maintain adequate visibility and is recommended to ensure that the border of the cyst opening is completely treated as well. Recommended settings are 30–55 W for CO_2 laser beam, 6–10 W for CO_2 fiber, and the use of the ablate function mode. *Plasma energy* has similar highlights, using a coagulation mode set at 10–40, with 5 mm average distance [40, 41]. When cyst eversion is not feasible, progressive exposition to apply the plasma at a perpendicular angle to the inner cyst surface is recommended. *Electrocoagulation* with different modes results in different levels of ovarian damage and should be used cautiously to avoid impairing ovarian reserve.

A Cochrane systematic review that identified two RCTs [42] concluded that cystectomy treatment may have improved outcomes regarding pain reduction, endometrioma recurrence rates, and spontaneous pregnancies among subfertile adults. However, concern was later raised regarding the negative impact of surgery on ovarian reserve, especially in women with bilateral endometriomas [43], large size endometriomas, and repeat endometrioma cystectomy procedures [39]. We advocate considering fertility preservation in such cases. Reduced levels of anti-Mullerian hormone (AMH) have been repeatedly shown following endometrioma excision at up to 9 months of follow-up. Interestingly, in a study of plasma jet ablation of the endometrioma with longer follow-up, of 18 months, partial recovery in AMH levels was demonstrated [44]. Due to the current data regarding the negative effect of excision on the ovarian reserve, the ablation technique should be considered in the adolescent patient. A combined two-step excisional ablation procedure was proposed [45, 46] to excise endometrioma larger than 5 cm (including combined cystectomy and ablation). This provides the opportunity for more accurate treatment of a smaller cyst in a second procedure and sparing of the ovarian reserve. A multicenter RCT that compared women with bilateral endometriomas >3 cm, between those treated by cystectomy and those treated by a combined excision/ablation technique using bipolar coagulation, reported higher recurrence rates following the combined technique (5.9% vs 2%), while antral follicle count did not differ at 1, 3, and 6 months of follow-up. The use of bipolar energy has been shown to significantly reduce AMH levels postoperatively compared to the use of hemostatic sealant or ovarian suturing [47].

Mullerian Anomalies – Surgical Aspect

Adolescent EM patients with malformations undergo surgery at a younger age (16.2 vs 19.0) and have more ovarian involvement of EM in the obstructive malformations (14/15, 93.3%) compared to patients without anomalies [3]. Both these

characteristics support the retrograde menstruation theory. In a study of females who attended a reproductive endocrinology clinic, the frequencies of EM were not significantly different between those with (136) and without (3420) Mullerian anomalies (19.8% and 19.1%, respectively). However, among those with obstructive Mullerian anomalies, the rate of EM was significantly higher (58%); this highlights the impact of the outflow obstruction factor in EM formation [48–51]. In a case series of five laparoscopically resected non-communicating functional uterine horns [52], one patient had severe EM (stage III), and 4/5 patients presented in adolescents (Table 36.2).

Table 36.2 Case series of unicornuate uterus with functional horn

Cate	Age at presentation	Presenting complaint	Preop imaging and management	Diagnosis	Management
1	15	2 years worsening dysmenorrhea	Minimal response to medical management Initial normal U/S Laparoscopy for pain found stage III endometriosis, resected Pain postop, U/S identified? obstructed uterine horn Confirmed on MRI	Right unicornuate uterus with functional horn	Laparoscopic resection
2	14	Severe pelvic pain	No response to medical management U/S suggestive of Dx Confirmed on MRI	Left unicornuate uterus with functional horn	Laparoscopic resection
3	16	Worsening dysmenorrhea	Diagnosed with MRI Drained at OR at referring institution Endometriosis noted The given Lupron Rx	Right unicornuate uterus with functional horn	Laparoscopic resection
4	17	2 years worsening dysmenorrhea	No response to medical Rx Initial U/S normal Diagnosis made at OR at referring institution MRI confirmed	Solitary right kidney Left unicornuate uterus with functional horn	Laparoscopic resection
5	31	Worsening dysmenorrhea over last few years Dyspareunia	No response to NSAIDs U/S queried didelphys with obstructed left horn, 1 cervix MRI: unicomuate uterus, obstructed left horn attached by fibrous stalk	Right unicornuate uterus with functional horn	Laparoscopic resection

Precise and appropriate diagnosis of the anomaly is recommended [53], possibly with the use of abdominal ultrasound, MRI, laparoscopy, transvaginal ultrasound, hysterosalpingography, and hysteroscopy [52]. Vaginoscopy can be used to identify a double cervix as in a didelphic uterus. Associated renal anomalies should also be ruled out (possibly with MRI). As mentioned, laparoscopy offers the best evaluation tool for peritoneal EM and is also an efficient treatment tool.

Surgically, the first step is anatomical restoration. Adhesiolysis is of high importance to reducing complications of the bowel and the bladder and mainly of the ureter. Next, the rudimentary horn should be identified. Intraoperative use of transvaginal ultrasound or hysteroscopy can confirm the suspected anomaly and its location – hysteroscopy also enables assessing communication with the rudimentary horn.

The next step is ipsilateral salpingectomy. Care should be taken to divide the mesosalpinges as close to the salpinges as possible, in order to preserve ovarian reserve as much as possible. This is followed by dissection of the anterior and posterior broad leaf, with care to remove the ureter laterally (the peritoneal window technique is helpful), and then dissection of the uterine vessels. The rudimentary horn cavity is identified by entering it and identifying the characteristic dark chocolate-like fluid. The rudimentary horn is then carefully dissected and removed in total, followed by suturing the layers of the remaining uterine wall. An antiadhesive barrier is appropriately placed. Finally, a repeat careful inspection of any remaining EM lesions and surgical treatment is warranted.

A Rare Entity – Premenarchal EM

This is a rare entity of special interest and considerably more difficult to diagnose than adolescent EM. Symptoms and lesions occur before menarche and during the thelarche phase [54]. In a series of five premenarchal girls [55], EM was diagnosed in the workup of CPP, with a negative gastrointestinal workup. Their breast development ranged from Tanner I to Tanner III. The surgical finding was red and clear lesions, and all of them were surgically treated by resection or ablation, or both. All reported lesser pain after surgery. Two had repeat laparoscopies 6 and 8 years after the first operation, with pathology-proven EM. None of the patients received antihormonal treatment post-surgery, until the onset of menarche. In this series, no patient had an outflow obstruction anomaly; this supports theories of EM formation other than retrograde menstruation. In an 11-year-old before menarche, an endometrioma was eventually treated with a minilaparotomy and excision of the cyst [56]. In a 9-year-old with cyclic pelvic pain, red and clear lesions were resected and confirmed to be EM [57].

Table 36.3 Rates of repeat laparoscopy

Reference (year)	Diagnosis number	Age at diagnosis (years)	Design	Mean follow-up	Number of repeat laparoscopy (%)
Roman (2010)	20	<21	Prospective	2.6 yrs	2 (10)
Yeung (2011)	17	<20	Prospective	23.1 mo	8 (47.1)
Tandoi (2011)	57	<22	Retrospective	5 yrs	11 (19.3)
Audebert (2015)	55	<20	Retrospective	97.5 mo	17 (32.1)

From Audebert et al. [7]

Surgical Outcome

Laparoscopic treatment of EM lesions is effective for reducing pain in adults with EM (ESHRE level A [1]) and in adolescents as well. In a small series of adolescents who underwent excisions of EM, 80% were either pain-free or greatly improved after surgery [28]. This is supported by other studies by Roman [13] and Yeung et al. [6]. In Dun et al.'s series [12], of 25 cases of rASRM I-III at 1 year after surgery, pain was resolved or improved in 80%. In contrast, in Audebert et al.'s series [7], with a mean follow-up of 97.5 months, only 23% reported complete or significant resolution of their pain symptoms.

Regarding *recurrence rates and repeat laparoscopy*, the data are limited. Tandoi et al. [58] showed 56% recurrence during a 5-year follow-up of 57 young women aged up to 21 years (only 34% of them were confirmed laparoscopically, and the remaining diagnoses were based on symptoms or ultrasound findings). However, no visual or histological evidence was found in Yeung [6] et al.'s series, in which 8 of 17 teenagers underwent repeat laparoscopy during 66 months of follow-up. In Audebert et al.'s series [7], 34% underwent a second laparoscopy due to pain. The observed recurrence rate of endometriomas was 37% and for DIE, 50%. Rates of repeat laparoscopy are summarized in Table 36.3.

Long-Term Fertility Outcome

An important concern in EM, especially in adolescents, is the problem of subfertility. In Audebert et al.'s series [7], 11 of 18 women who desired pregnancy were subfertile; 6 of these 11 (55%) achieved a live birth (2 following in vitro fertilization). In a study with a mean follow-up of 8.6 years, among 28 of 52 (54%) adolescents with EM, a strong correlation was observed between fecundability rates and initial stage of disease: 75%, 55%, 25%, and 0% for stages I, II, III, and IV, respectively [59]. Table 36.4 shows the limited data known today about adolescent EM and impairment of fertility throughout life.

Table 36.4 Long-term fertility

Long-term fertility assessment in 135 young women diagnosed with endometriosis in adoblesence				
Authors and references	Patients	EM stage I and II	EM stage III and IV	Follow-up
Wilson-Harris BM et al. (2014) [68]	28 women aged 18–25 years	60.7% 28.6%	28.6%	Twenty women (714%) had at least one pregnancy during follow-up, which resulted in a live birth, of which >80% were spontaneous without the use of assisted reproductive technologies
Ventolini G et al. (2005) [59]	52 adolescents aged 12–18 years	14.3% 39.3%	42.8% 3.6%	Differences in fertility rates between stages were statistically significant: Stage I (75%), Stage II (55%), Stage III (25%), Stage IV (0%) ($p < 0.05$). Rates of spontaneous abortion were not statistically significant
Audebert A et at. (2015) [7]	55 adolescents, aged 12–19 years (mean age 17.8 years)	Total: 60%	Total 40%	Eighteen patients wished to have a child. Thirteen had a delivery (72.2%) and nine pregnancies occurred in patients who initially presented with Stage I to II endometriosis. Of the 11 patients who had subfertility, 6 successfully conceived (54.5%)

From V. de Sanctis et al. [36]

In summary, pain seems to improve in a high proportion of adolescents with EM postoperatively. Recurrence of pain or disease is a substantial problem. Initial long-term fertility data are reassuring for the majority of adolescents diagnosed with early stage disease, yet seem devastating for advanced, stage IV, disease. This suggests that if early surgical intervention could reduce the likelihood of progression to stage IV disease, it could improve fertility outcome.

Benefits of Early Surgical Intervention

The importance of early diagnosis is highlighted by the clear possibility that EM is a *progressive disease* in its nature. Though a matter of debate, a number of studies support this notion. Disease progression has been reported in second-look laparoscopies after ablative treatment for adolescent EM, with at least 6-month intervals [18]. In the follow-up data of Audebert et al. [7], 9 of 50 adolescents were identified with DIE at repeat laparoscopy (not seen initially), and an additional 5 new cases of endometrioma were identified, thus indicating disease progression. Compared to women without DIE, adult women with DIE were more likely to report absenteeism from school during menstruation in their adolescence and to report a history of early and prolonged use of oral contraception pills for dysmenorrhea [60]. This implies

that the root of DIE may be during adolescence, and supports a theory of disease progression, from underdiagnosed EM during the adolescent period.

Despite the risks of surgery – a repeat surgical intervention, recurrence of disease, and potential ovarian reserve damage – for certain adolescents, such as those not responding to medical therapy and whose daily activities are severely affected, with detrimental social and psychological impact, laparoscopy should be considered. This approach is supported by the diagnostic and treatment capabilities of laparoscopy. In our view, observed rates of repeat laparoscopy should not deter appropriately timed surgery when indicated, at a center of expertise. The alternative is to stand by while the patient suffers. The majority of patients would benefit from a substantial improvement in their quality of life, together with the other benefits associated with a confirmed diagnosis. These are not to be dismissed, even if during follow-up a need for repeat laparoscopy arises.

Postoperative Therapy

Postoperative therapy is aimed at preventing disease progression, recurrence of symptoms, and endometrioma and at reducing pain in the event of suboptimal treatment [61]. Treatment modalities include combined oral contraception, progestins, and GnRHa.

In a retrospective series of 90 adolescents and young women aged 12–24 years, who received hormonal suppression (oral contraceptives, GnRHa with add-back, or continuous progesterone) after initial laparoscopic diagnosis [62], a second laparoscopy showed no change in stage for 70%; improvement by one stage for 19%, and by two stages in 1%; and worsening by one stage in only 10%.

A very small series demonstrated the possibility of EM progression when no hormonal suppression was taken [63]; this highlights the importance of further treatment. All three patients in a case series who were noncompliant to postoperative therapy and who underwent a second laparoscopy developed a more severe stage of disease.

A retrospective analysis of adolescents in China showed a possible decrease in recurrence rates following postoperative treatment with GnRH [3]. In that study, recurrence did not occur in any of the five adolescents treated postoperatively with the GnRH analogue compared to 60% of those who did not receive any medical treatment and 47% of those treated postoperatively with oral contraceptives. The risk of impaired bone density following long-term use of GnRH analogue is of concern. Thus, concomitant add-back therapy is presently recommended, based on the hypothesis that low levels of estradiol would suffice to suppress endometrial implants, but also to maintain bone density with relief of vasomotor symptoms [64, 65]. Even among adolescents, the use of intraoperative placement of the levonorgestrel-releasing intrauterine system (LNG-IUS) could be considered a means of postoperative medical therapy. This is especially suitable for patients with a need for contraception and with difficulty complying with medical treatment and

has been shown to decrease the duration of pain and bleeding [66]. More evidence is needed regarding the effectiveness of postoperative treatment, for which the data are inconclusive.

Current knowledge has led to *a general consensus that adolescents with laparoscopically confirmed EM should receive medical treatment after surgery*. There is no consensus as to the best postoperative medical treatment therapy modality and duration.

Another aspect of postoperative treatment and care is continued follow-up and psychological intervention. In a study from Puerto Rico of 24 adolescents and young women with surgically confirmed EM [67], mental health status and quality of life impact were assessed and the association with different coping strategies was evaluated. This study demonstrates the substantial impact of EM symptoms on the psychological well-being of these patients and identifies opportunities for psychological interventions (behavioral cognitive, rational/emotive therapy) to restructure coping styles that lead to improved quality of life.

Summary

Surgical treatment in EM is challenging, and this is especially true in adolescents. The surgeon must be familiar with the characteristics of this age group – employing extra caution upon abdominal entry and devoting special attention to identify the typical and atypical lesions, including biopsies to confirm the diagnosis. We encourage video and image recordings. Endometrioma must be treated with care to minimize impairing ovarian reserve. The surgeon's responsibility is particularly heavy, awarding proper diagnosis and surgery, support, and reassurance. Medical treatment is advised, and attentive follow-up is needed to detect recurrence. A well-timed surgery of the appropriate patient, at an expert center for EM, has a major impact on an adolescent's life, including physical, social, and psychological aspects.

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Chapter 37
The Role of Hysteroscopy in Adolescent Gynecologic Evaluation and Treatment

Nili Raz and Sergio Haimovich

Hysteroscopy—Background

Hysteroscopy is a minimally invasive approach, using a small endoscope to view and treat common gynecologic problems. Hysteroscope is introduced into the uterus via the vagina and cervix, allowing visualization of the endometrial cavity, tubal ostia, endocervical canal, cervix, and vagina. The *reasons to perform hysteroscopy* include both diagnostic and therapeutic indications (Table 37.1).

Hysteroscopy ideally would not be performed in women with an active diagnosis of cervical or uterine carcinoma, a viable desired pregnancy (unless used to remove an IUD in this pregnancy), or an active pelvic inflammatory infection.

Historical Development of Hysteroscopy

Lichtleiter, or "light conductor," was the name of the first light-assisted device, invented by the pioneer scientist Philipp Bozzini in the beginning of the nineteenth century. Later on, in 1853, Antonin Jean Desormeaux developed a cystoscopic device and coined the term "endoscopy." In 1869 pantaleoni used a modification of Desormeaux's endoscope to inspect the uterine cavity, diagnose, and treat his patients.

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Table 37.1 Diagnostic and treatment indications for hysteroscopy

Foreign bodies (such as IUDs)—removal	Postmenopausal bleeding
Mullerian anomalies—septum resection and/or transection	Asherman syndrome/adhesions with adhesiolysis
Polyps—resection	Sterilization
Myomas—resection and enucleation	Adenomyosis
Residual products of conception—removal	Vaginal/cervical endometriosis
Dysfunctional/abnormal uterine bleeding	Infertility investigation
Endometrial hyperplasia	Fetal malformation diagnosis in miscarriages
Endometrial carcinoma	Cesarean scar/hysterotomy defect assessment and repair
Cervicitis and endometritis	Cervical stenosis repair

Throughout the twentieth century, there has been progressive improvement on this core endoscopic invention through improved optics, smaller caliber hysteroscopes, variations in flexibility and durability, and distention media enhancing visualization. Particularly critical to office hysteroscopy has been blending vaginoscopy with smaller caliber, as up to a third of adults cannot complete diagnostic office hysteroscopy with a 5 mm hysteroscope (Campo 2005). This is even more of an issue in the pediatric population, where the nulliparous cervical lumen is meaningfully smaller than the parous cervix, and the prepubertal cervical lumen has an even more narrow caliber.

Over the years, clinical experience has increased and smaller diameter hysteroscopes have been produced. This enabled performing more procedures in an outpatient clinic setting and made this important technology common and popular.

This reduction in hysteroscopic caliber facilitates examination of the vagina, cervix, and uterine cavity, minimizes pain, and can preserve the hymen, in cases where the anatomic integrity of the adolescent's hymenal tissue is important, due to a religious or cultural point of view or other reasons. Explaining these advantages engages the patient and her family, reduces delay in diagnosis and treatment, and increases patient satisfaction. *Johary* et al. reviewed 11 articles, which described operative hysteroscopies performed on 12–17 years old adolescents, with no hymen injury during the surgery [1–3] (Fig. 37.1).

Timing of Hysteroscopy

The preferred time for hysteroscopic visualization of the endometrial cavity is at the mid-follicular phase, just after cessation of menses. Though secretory phase hysteroscopy can be performed after ruling out pregnancy, there is the risk of thick endometrium appearing like endometrial polyps and increasing endometrial edema formation during the procedure. It is more challenging to perform a hysteroscopy during menstruation, since blood may blur visibility. It is possible to prime the endometrium pharmacologically, usually by combined or progesterone-only contraceptives [4–6].

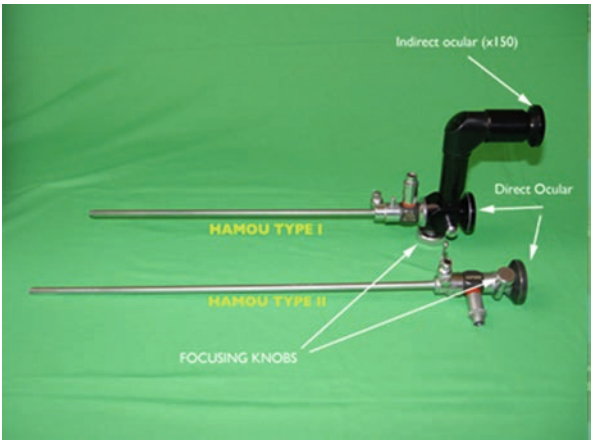

Fig. 37.1 Hamou's microcolpohysteroscope, Photo published with permission from Dr. Luigi Montevecchi

Cervical Preparation

Hysteroscopy requires cervical dilation for the hysteroscope to enter the cervix, but not excessively for prevention of distention media outflow through the cervix. Almost 50% of the complications during hysteroscopy are associated with the hysteroscope passage through the cervix. The use of narrow caliber or flexible hysteroscopes, especially in premenopausal women, reduces the need for cervical dilatation. Histories of cervicitis, cryotherapy, vaginal nulliparity, and pre- or postmenopausal status are all risks for cervical stenosis. Pharmacological cervical ripening (e.g., misoprostol 200–400 mcg orally 2–24 hours prior to the procedure) is a good possibility for this purpose, reducing the risks as well as minimizing the mechanical dilation during the procedure. When administering misoprostol, one must prepare the patient for possible side effects, such as vaginal bleeding, abdominal cramps, diarrhea, nausea, and fever. It is advised to avoid mechanical cervical dilatation as much as possible, in order to lower pain, false route, perforations, and possible future cervical incompetence [7–11]. Laminaria and vaginal pharmacological dilatation are possible, but less preferable, in adolescent patients. Similarly, vasopressin use (where permitted) may reduce the force necessary for cervical dilation but may have limited tolerance in the conscious pediatric patient.

Anesthesia

Cheong et al. recommended intravenous sedation to reduce patient anxiety and pain, decrease vasovagal reactions, relax the buttocks muscles, and reduce the risk of hymenal laceration or injury [12]. Oral sedation remains a reasonable alternative for the anxious pediatric patient, particularly with diagnostic hysteroscopy; however, weight-adjusted dosing is imperative where appropriate.

Instrument Choice

Equipment parameters often relate to operative goals. Diagnostic flexible hysteroscopes can have "all in one" telescope, camera, light source, and a single lumen inflow channel that can also be used for an operative channel. However, inflow can often be occluded with concurrent instruments. Rigid telescopes are more likely to have separate camera and light source attachments and typically fit inside combined or separate inflow and outflow sheaths. Though camera heads typically project the signal to a remote monitor, some single-use hysteroscopes have the monitor in the handheld portion of the hysteroscope. A variety of distention media can be used with hysteroscopy, where saline has increasingly replaced alternatives such as carbon dioxide gas and glycine [13].

Outer Diameter

The outer diameter of a hysteroscope refers to the maximum width of the sheath in which the telescope and all instruments are inserted, including channels for distention media and all instruments. It typically ranges from 2.7 to 10 mm. Advantages of minimizing the outer diameter include reduction of patient pain, discomfort, and need for anesthesia, especially when hymen preservation is required. It will be discussed later on in this chapter. When the OD exceeds 5 mm, anesthesia is common. However, even with smaller calibers, anesthesia may be needed depending on the anatomy, intervention, and the patient's maturity and pain tolerance.

Working Length

The working length of a hysteroscope refers to the length from the eyepiece to the distal tip. It ranges from 160 to 302 mm.

Telescope

A telescope consists of an eyepiece, a barrel, and a lens. The larger the outer diameter, the better the quality of visualization. Images have classically been transmitted through optical fibers to a monitor or other screen. An emerging alternative is chip-based cameras which pick up an image at the distal tip of the hysteroscope that is transmitted to the intended display. This allows for 1080p and even 4K level resolution or, if holding the resolution constant, a smaller caliber for the hysteroscope for the same image quality.

Though hysteroscopes typically range from 0 to 70 degree angles, commonly a 30-degree hysteroscope is frequently used for a panoramic view. In a 30-degree hysteroscope, using a fulcrum effect as well as rotation allows for comprehensive view of the uterine cavity. Flexible hysteroscopes typically have a 0-degree angle, where flexion of the distal tip allows cornual visualization when not readily achieved.

Light Source

Hysteroscopes are typically connected through an optic fiber to a cold light fountain. Though single-use hysteroscopes as well as "all in one" flexible hysteroscopes often dispense with separate cabling for a light source, this occasionally leads to suboptimal brightness. Digital correction can sometimes offset this issue.

Operative Instrumentation

Given the diversity of surgical needs, a vast array of instruments are available, including, but not limited to, forceps, scissors, tenacula, morcellators, lasers, resectoscopes (using monopolar or bipolar energy), cutting loops, and coagulating rollerballs.

Distention Media

Given that the uterine cavity is a potential space rather than an actual one (in that the walls are typically adjacent), distention is necessary for visualization. The ideal distension media should be are nonconductive (for preventing thermal injury) and nontoxic, allow clear assessment, also cheap and isomolar (for preventing electrolyte imbalance complications if absorbed by the bloodstream) and cleared rapidly from the body. With these goals in mind, the most commonly used distention media are electrolyte neutral solutions (normal saline, lactated Ringer's) or electrolyte-poor solutions (5% dextrose, 1.5% glycine, 3% sorbitol, and 5% mannitol). In the past, carbon dioxide was also used.

Electrolyte neutral media can be used with bipolar energy, laser, or mechanical energy such as morcellators. It is contraindicated to use monopolar energy in this conducting environment. Electrolyte-poor solutions may be used with monopolar energy. Given advances with bipolar and morcellation technology, saline is increasingly used for distention. Conversely, carbon dioxide and 32% dextran are becoming rarer, the latter in part not only from complications, but also because of the associated mess affecting instruments [13–18].

It is important to monitor fluid deficits to minimize the risk for volume overload. Office diagnostic hysteroscopy can often be performed with total infusion volumes

of 20–200 mL, which is well below American Association of Gynecologic Laparoscopists (AAGL) guidelines. These recommendations recommend 2500 mL maximum of isotonic media for healthy women and 1500 mL of hypotonic media for healthy women. However, for patients with cardiac compromise, a maximum of 300 mL isotonic media may be necessary and none of these guidelines are weight adjusted for pediatric patients. When performing operative hysteroscopy, where cases can be longer, and particularly cases such as type 2 myomectomy where there is greater risk for extravasation and systemic uptake, these limits are easier to reach. The American College of Obstetricians and Gynecologists advocates the use of an automated fluid pump and monitoring system [19]. If using a pressure bag instead of automated infusion, there is debate as to at what point inflow pressure is excessive. This is a difficult debate to resolve owing to the heterogeneity of patients. Patient sedation and analgesia, cervical patulousness, procedural duration and invasiveness, patient age, maturity, and pain tolerance can all play a role in finding this ideal balance.

Hymen Preservation—Background and Assisting Maneuvers

The 2015 review of *Johary* et al. [3] showed that a hysteroscope is useful for vaginoscopy or hysteroscopy for the exploration of the immature genital tract and may help in the diagnosis and treatment of gynecologic disorders in adolescent patients with an intact hymen, limited vaginal access, or a narrow vagina [3].

Virginity is a personal issue influenced by culture, origin, religion, and personal or family decision. It is important that the medical staff respect this. Advancing the endoscope into the vagina and uterus without a speculum or tenaculum allows the hysteroscopist to assess reproductive organs safely and atraumatically. Thus, even though virginity, in patients to preserve it, is a limiting factor for many other gynecologic diagnostic modalities, it is not a limitation for hysteroscopy. Note that a rigid hysteroscope may be used as a vaginoscope. In Tansu Küçük's 2007 review on hymen preserving hysteroscopy [20], he describes an operative technique:

> The patient was placed in hyperflexion lithotomy, in order to lower the uterus, thus allowing less movement of the hysteroscope. The hysteroscope entry was at 12 o'clock, just below the urethra, and an assistant held the hysteroscope in place with his or her index finger, paying continuous attention to hymen safety. Wide movements should be avoided during manipulation. Most patients were sedated or anesthetized; a 2.9-mm, 30-degree rigid telescope with an operative sheath of 3.5 mm was used for the examination (Karl Storz, Germany). When needed, the operative instruments used were hysteroscopic grasping forceps and hysteroscopic scissors; distension medium was a normal saline solution in continuous-flow mode. Vaginal distention was achieved by squeezing the vulva and labia together. No speculum or tenaculum was used in the "no-touch technique" as described by Bettochi et al. [20, 21].

Xu et al. [22] described the use of a rigid hysteroscope to diagnose and treat patients who were virginal. They describe maneuvers to preserve the hymen when the uterus is retroverted or anteverted (the cervix is usually not straight beyond the

hymenal ring in those types of uteruses). If the uterus was acutely anteflexed, they suggested the bladder should be fully distended and pressure should be applied to the pubis symphysis, to reverse the anteflexed uterus. In retroflexed uteruses, they suggested to apply pressure to move the uterus to the mid-pelvic position by using a finger in the patient's rectum [22].

The use of a 3.5 mm diameter hysteroscope in a diagnostic setting has been shown in RCTs and guidelines to be associated with a decrease in pain and in the number of failed procedures, when compared to a 5 mm hysteroscope [23, 24]. Smaller outer diameter hysteroscopes are associated with a decrease in the need for anesthesia or mechanical dilatation, decreased pain levels, and increased patient comfort. Procedures requiring outer diameter of less than 5 mm can be done without anesthesia, while procedures requiring a hysteroscope wider than 5 mm will most probably require anesthesia and sometimes mechanical cervical dilation in an operating room [23]. Given that the nulliparous cervical lumen can average 2.7 mm, further reducing hysteroscope caliber minimizes difficulties in cervical dilation with an intact hymen. Moreover, using a flexible hysteroscope facilitates traversing the cervix without a fulcrum effect, where manipulation can be done at the distal tip, without having to move the length of the hysteroscope up or down with potential risk for hymenal trauma.

Operative Setting

Hysteroscopy may be performed in the office/outpatient clinic with minimal or no anesthesia or in the operating room with or without anesthesia. An ambulatory setting is cost-effective and convenient and allows the patient to view and be educated about her own reproductive tract. There are failures, mostly due to pain or anxiety, so that careful patient selection should be performed, obtaining consent, managing expectations, especially with adolescents who might be more prone to vasovagal episode and pain reactions. However, in the adult setting without analgesia (other than ibuprofen or acetaminophen if desired), it has been shown that with small caliber (<3 mm) flexible endoscopes, 91% of women have mild to no discomfort with diagnostic hysteroscopy and only 1% have severe or extreme discomfort. When hymen preservation is needed, an operating room with sedation is recommended [25, 26]. Antibiotics are not needed for most hysteroscopic procedures [13].

Surgical Technique

When using an up to 4 mm OD hysteroscope, after placing the patient in dorsal lithotomy position and inflowing the distention media, the surgeon may enter the cervical canal under direct visualization for better navigation, noting and describing the vagina and the cervical appearance (both the internal and external os and the cervical canal). When anesthesia is administered, or if a wider diameter hysteroscope is used, such as in cases where hymenal preservation is not an issue, the surgeon can use a speculum,

tenaculum, and dilators for an easier approach to the cervix. It is important not to dilate the cervix above the hysteroscope OD, to prevent excessive outflow of distention media. Once entering the uterine cavity, the surgeon should observe and document the cavity structure, the endometrial lining, and the ostia and look for lesions, polyps, myomas, adenomyosis, Mullerian anomalies, or any uterine abnormalities.

Complications

Hysteroscopy is a safe procedure, especially when performed in office. The most common perioperative complications are associated with operative hysteroscopy which includes mechanical dilatation that is rarely needed when using a small diameter hysteroscope. These complications are hemorrhage (2.4%), uterine perforation (1.5%), and cervical laceration (1–11%). Other less common complications include fluid overload, visceral injury, infection, air embolism, and, rarely, death. Delayed complications may include intrauterine adhesions and infertility [19]. These complications are rare in diagnostic hysteroscopy when using a narrow OD hysteroscope [27].

Gynecologic Exam in Adolescents

A hysteroscopic approach to examining an adolescent's vulva, vagina, and uterus allows no speculum or tenaculum use, which is an important factor in the gynecologic exam of an adolescent, since in many adolescents, the hypoestrogenized vulva and possible hymen hinder instrumentation.

The most common referrals of adolescents to a gynecologist relate to bleeding irregularities or discharge. Less common causes are vulvar pruritus, abdominal/pelvic pain, dysmenorrhea, congenital anomalies, foreign bodies, trauma, abuse, and, rarely, malignancies [3, 28, 29]. The 2018 ACOG Committee opinion summary on Dysmenorrhea and Endometriosis in the Adolescent states that dysmenorrhea experienced by adolescents is most frequently primary dysmenorrhea. The most common cause of secondary dysmenorrhea is endometriosis [30]. Cases of abnormal bleeding or persistent vulvovaginitis require vaginal examination, as well as a suspected foreign body or structural anomaly. Visualization or palpation using conventional methods such as small-sized specula, nasal specula, pediatric cystoscopes, and even otoscopes has been described for this purpose. Bimanual exam might be traumatic and cause lacerations. These options allow limited visibility. Imaging studies such as a 3D US or MRI allow more information, yet they are not always accessible and may not be diagnostic for many gynecologic problems. The 2018 ACOG Committee opinion summary on Dysmenorrhea and Endometriosis in the Adolescent discusses the possible reasons for secondary

dysmenorrhea and states that any obstructive anomaly of the reproductive tract, whether hymenal, vaginal, or other Mullerian anomalies, can cause secondary dysmenorrhea, and, as mentioned earlier, the most frequent reason for secondary dysmenorrhea in adolescents is endometriosis. For this reason, European College of Obstetrics and Gynaecology (ECOG) suggests that, regardless of the findings of a pelvic examination, pelvic imaging with ultrasonography be considered during evaluation of secondary dysmenorrhea. In addition to the last statement, we suggest hysteroscopy as an essential and integral part of such evaluation. Hysteroscopes allow excellent visualization of the vagina, cervix, and uterus, as well as the interventional therapeutic options for metroplasty, foreign body extraction, etc. ECOG also recommends inserting a levonorgestrel-releasing intrauterine system (LNG-IUS) under anesthesia to patients undergoing diagnostic laparoscopy for evaluation of dysmenorrhea or chronic pelvic pain. Further research is needed on the possibility to insert a levonorgestrel-releasing intrauterine system (LNG-IUS) under hysteroscopic guidance, using a hysteroscopic grasper, possibly with abdominal US guidance, thus eliminating the need for a speculum. We found no article describing such technique [3, 22, 30, 31]. It is feasible to perform both hysteroscopy and laparoscopy in adolescents, as described in several articles, such as by El Saman et al. (2011) [29]. This may be especially useful when endometriosis is suspected. Another therapeutic option of hysteroscopy in dysmenorrhea secondary to septum or anomaly is resecting the obstruction using resectoscope or laser device. Gezginç et al. reported leaving a pediatric Foley catheter to prevent adhesion of vaginal septum and showed this was safe for hymen preservation [32]. Alternatives to Foley placement to reduce postoperative adhesions include tampon, vaginal dilators, or second-look office hysteroscopy with sweeping of adhesions were they to form [32, 33].

The Possible Role of Hysteroscopy in Patients with Suspected Endometriosis

There is a well-researched and tight relationship and coexistence between endometriosis, adenomyosis, and uterine leiomyoma, possibly affecting the severity of symptoms. Adenomyosis is a benign presence of ectopic endometrial glands within the uterine myometrium, in a diffused or focal form. The focal forms are described as adenomyotic cysts or adenomyomas [34, 35]. Brosens et al. [36] reviewed 17 articles describing 21 adolescent patients between the ages of 13 and 20, where all but one had pathologic findings of adenomyosis (mostly treated due to pelvic pain dysmenorrhea, refractory to conservative drug treatment). They demonstrated that cystic adenomyosis is more relevant to adolescents and even suggested a pathologic classification system in which the category “Endometrial Lined Myometrial Cysts” is almost specific to adolescent and young women [36]. Autopsies performed on children aged 4–14 also found cases of adenomyosis [35].

Adenomyosis often coexists with uterine diseases, such as uterine leiomyomas and endometriosis, and its treatment may reduce the severity of symptoms [37–40]. Though adenomyosis is considered a rare diagnosis in adolescents (and a more frequent diagnosis in women in their 30s and 40s), it is recommended to consider it in the differential diagnosis of dysmenorrhea and chronic pelvic pain in adolescents [41, 42]. We believe that the diagnosis of adenomyosis might be underestimated in adolescents, since diagnostic measures such as MRI and hysteroscopy are not frequently performed in this age group.

The role of combining hysteroscopy and laparoscopy in patients undergoing laparoscopy due to chronic pelvic pain has been previously studied. Nezhat et al. [44] found that the most frequent finding in these patients was endometriosis, and when endometriosis was the primary finding at laparoscopy, hysteroscopy revealed abnormalities in 32.5% [44]. Carter documented similar results diagnosing hysteroscopic abnormalities in 30% of patients who underwent laparoscopy and hysteroscopy due to primary compliant of chronic pelvic pain [45].

The retrograde menstruation theory suggests that outflow obstruction that may occur in Mullerian anomalies can be associated with endometriosis formation [43]. It is also known that ectopic endometrial implants, though mostly located in the pelvis, can also be present in other reproductive organs such as in the uterine cervix, vagina, and vulva (see Figs. 37.2, 37.3, and 37.4). Given that diagnostic hysteroscopy can often be performed gently without anesthesia and abdominal incisions, and recognizing the trend to perform less invasive and office-based assessment prior to more invasive approaches, there are meaningful opportunities to integrate

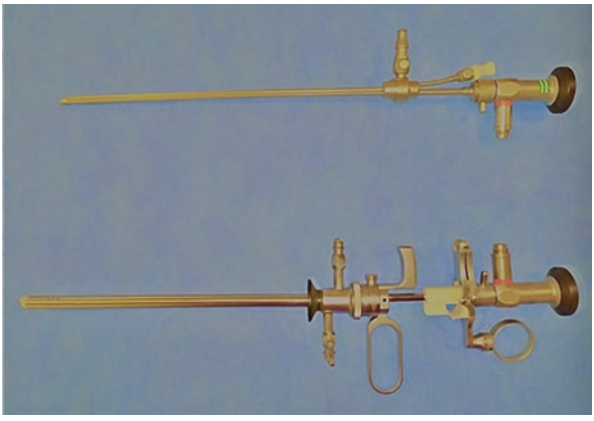

Fig. 37.2 A 5 mm and a 10 mm hysteroscope used in authors operating room

Fig. 37.3 A 30-Degree telescope used in authors operating room

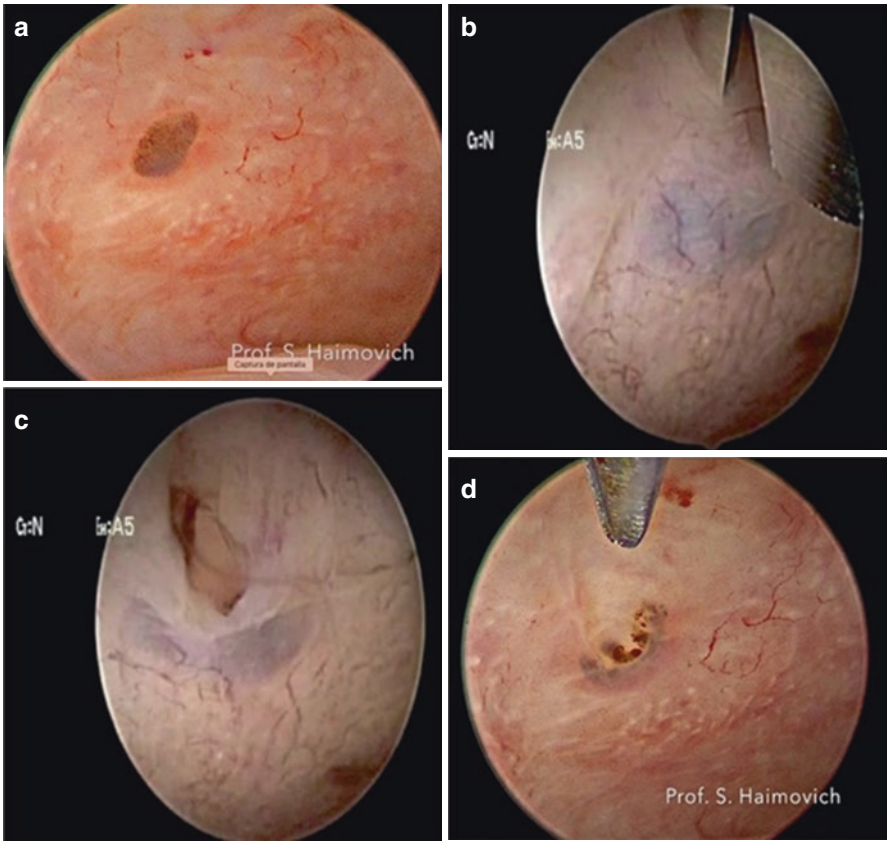

Fig. 37.4 Hysteroscopic view of adenomyosis

hysteroscopy into the evaluation and treatment of endometriosis workup in both adults and adolescents.

Summary

Sir William Osler noted that "the good physician treats the disease, but the great physician treats the patient who has the disease." The goal in managing adolescents with endometriosis is to alleviate pain in a manner that is as accurate, minimally invasive, and effective as possible. Excluding foreign body effects on pediatric pelvic pain, identifying Mullerian anomalies exacerbating menorrhagia, recognizing adenomyosis, and more—all of these fall within the spectrum of opportunity afforded through hysteroscopy for optimal care in a vulnerable population. With technology having advanced to the point where hysteroscopy in almost all

circumstances can be done accurately, gently, safely, and quickly, the true remaining question is why we do not perform it more often.

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Chapter 38
Nutrition and Lifestyle Factors

Lauren Manaker and Ceana H. Nezhat

Endometriosis is an ancient condition that has been explained in detail in other chapters of this book [1]. Although it affects a large percentage of women, the complex etiology is still unclear [2].

Genetic, environmental, and lifestyle factors appear to be associated with the development and maintenance of endometriosis [3]. There is evidence that food and nutrients influence both the pathogenesis and progression of the disease, leading to the possibility of alternative, adjuvant treatments to those suffering from the disease [3]. Among the environmental aspects, nutrition has not been substantially explored in well-designed studies, despite evidence suggesting its impact on the risk of developing as well as symptoms and outcomes associated with the disease.

One of the most basic recommendations and possibly one of the most effective ways to reduce the risk of developing many diseases is to increase consumption of fruits and vegetables. Fruits and vegetables provide vitamins, minerals, phytochemicals, antioxidants, and other substances that protect against a variety of chronic diseases [4–6]. In addition to essential micronutrients, fruits and vegetables contain thousands of biologically active phytochemicals that are likely to interact in a number of ways to prevent disease and promote health [7]. Fruits and vegetables are also rich in antioxidants, which help protect the body from oxidative damage.

It is recommended that Americans consume between 1.5–2 cups per day of fruits and 2–3 cups per day of vegetables according to the Centers for Disease Control and Prevention [8]. The Dietary Guidelines for Americans 2010 and MyPlate recommends Americans fill half of their plate with fruits and vegetables [9]. Despite the evidence regarding the benefits of fruit and vegetable consumption, only 12 and 9% of Americans met the recommended amount of fruits and vegetables per day, in 2015, respectively [8].

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Few studies have explored the influence of nutrition on endometriosis risk, even though numerous books and websites suggest dietary changes for the prevention and control of endometriosis [10]. Research suggests that fruit and vegetable intake is inversely related to risk of developing endometriosis.

Fruits and Vegetables

Fruits and vegetables in general contain many features that cannot be replicated in pill form. The first scientific article addressing the subject was published in 2004, by Parazzini et al., who evaluated 504 women between the ages of 20 and 65 years, using a food frequency questionnaire. They found that the highest weekly intake of fruits and vegetables was inversely associated with risk of developing endometriosis [11].

To investigate fruit consumption's role in endometriosis risk further, investigators utilized data from the Nurses' Health Study II cohort (NHS II cohort) established in 1989 as a large prospective cohort of nurses following the original Nurses' Health Study (in which the original subjects were no longer considered "young" since it was established in 1976). Married registered nurses between the ages of 25 and 42 years were included. Nurses were selected as subjects due to their ability to report medical information accurately. In total, 116,430 women were included in the Nurses' Health Study II cohort [12].

Two thousand six hundred and nine cases of endometriosis were reported from the NHS II cohort. Researchers investigated the relationship between fruit and vegetable intake and endometriosis risk. Utilizing a food frequency questionnaire and found an inverse relationship between higher fruit intake and diagnosis of endometriosis. Specifically, consuming one or more servings of citrus fruit (like oranges, grapefruits, or lemons) had a 22% lower endometriosis risk compared with women who consumed fewer than one serving of these fruits (95% CI = 0.69–0.89; $P_{\text{trend}} = 0.004$) [13].

One surprising finding from this study was that consumption of one or more servings of cruciferous vegetables (like broccoli or Brussels sprouts) was associated with a 13% higher risk of endometriosis compared with those consuming less than one serving of these vegetables (95% CI = 0.95–1.34; $P_{\text{trend}} = 0.03$) [13].

When specific nutrients were analyzed, consumption of the carotenoid beta-cryptoxanthin was significantly related to lower endometriosis risk (RR fifth quintile = 0.88, 95% CI = 0.78–1.00, $p = 0.02$) [13]. Beta-cryptoxanthin is found in large amounts in only a small variety of foods. Foods rich in beta-cryptoxanthin include tangerines, persimmons, red peppers, pumpkins, and oranges [14].

Findings from studies regarding individual micronutrients include:

- Vitamins C and E act as antioxidants, which may help inhibit growth and adherence of endometrial cells [15].
- Pyridoxine (vitamin B6) supports the conversion of linoleic acid to gamma linolenic acid. This conversion is key to the production of certain anti-inflammatory prostaglandins which may inhibit the growth of endometriosis tissue [16].

Table 38.1 A list of good sources of the specific nutrients mentioned in this study to encourage intake

Thiamine (vitamin B1)	Trout, black beans, mussels, acorn squash
Folate (vitamin B9)	Spinach, asparagus, avocados, romaine lettuce, black-eyed peas
Vitamin C	Orange, kiwi, grapefruit, red pepper, strawberry
Vitamin E	Almonds, hazelnuts, jackfruit, peanuts
Niacin (vitamin B3)	Milk, eggs, peanuts, chicken
Pyridoxine (vitamin B6)	Chickpeas, yellowfin tuna, sockeye salmon, banana
Cobalamine (vitamin B12)	Clams, beef liver, rainbow trout, sockeye salmon

Several studies show no effect of specific nutrients on endometriosis. Findings include:

- No effect of vitamin E intake on any endometrial parameters [15].
- No effect of thiamine, niacin, pyridoxine, folate, cobalamine, vitamin C, and vitamin E on endometriosis risk [17].
- Increased β-carotene consumption was associated with increased endometriosis risk [17].

The effect of individual micronutrient intake (supplemental not whole-food form) on endometriosis diagnosis has been examined utilizing a sample size of 1383 women diagnosed with endometriosis from the NHS II cohort.

Intakes of thiamine (B1) (RR = 0.84, CI = 0.72–0.99; $p = 0.04$), folate (B9) (RR = 0.79, CI = 0.66–0.93; $p = 0.003$), vitamin C (RR = 0.81, CI = 0.68–0.95; $p = 0.02$), and vitamin E (RR = 0.70, CI = 0.59–0.83; $p < 0.0001$) solely from food sources were inversely related to endometriosis diagnosis. However, intakes of these nutrients from supplements alone were unrelated to endometriosis. Intakes of niacin (vitamin B3), pyridoxine (vitamin B6), and cobalamine (vitamin B12) from foods remained unassociated with endometriosis diagnosis risk. Vitamin C intake from food had an even greater effect on endometriosis risk when the data was stratified for smokers [10]. Table 38.1 shows a list of foods that are good sources of specific nutrients.

Since the results of this study varied from the trend of previous studies, the authors hypothesize that intake from whole-foods has a different effect on outcomes due to patterns of diets rich in these vitamins (like fruits and vegetables). The benefits may not stem from the vitamin itself, but the well-balanced diet as a whole [10].

Retinoic Acid

It is difficult to attribute reduced risk or improved symptoms of endometriosis to one nutrient [18], likely due to a combination of many features that these foods possess. Retinoic acid is found in many colorful fruits and vegetables and has various functions in cells, including a possible role in endometriosis development [19]. The endometrium is rich in retinoic acid. Retinoid signals are involved in the

development and maintenance of the endometrium, stromal decidualization, and blastocyst implantation. Moreover, aberrant retinoid metabolism seems to be a critical factor in the development of endometriosis [20]. Reduced retinoic acid concentrations are observed in endometriotic lesions [21]. All-trans-retinoic acid (ATRA) in the body is made of vitamin A and helps with cell development and growth [22]. Investigation into mRNA expression levels in ATRA-treated endometriotic stromal cells concluded that retinoic acid has the potential to suppress endometriosis development [19].

In one recent review article investigating retinoid's role in endometriosis development and treatment, the authors concluded that "the precisely controlled retinoid signaling may play a critical role in a number of important endometrial physiological events. In addition, the altered RA pathway may be a leading cause for the histogenesis of endometriosis" [20]. It has been reported that women with endometriosis have lower intake of vitamin A than women without endometriosis [13]. Therefore, encouraging intake of vitamin A-rich food, particularly foods rich in retinoic acid, is recommended. Foods rich in retinoic acid include:

- Dark green vegetables
- Yellow vegetables
- Red vegetables
- Red and yellow non-citrus fruit
- Certain fish like sardines and cod
- Liver

Resveratrol

Resveratrol is a polyphenolic plant compound that acts like an antioxidant. It is found naturally in certain foods, including:

- Red grape skin
- Peanuts
- Blueberries
- Dark chocolate

In animal models of endometriosis, resveratrol supplementation has been shown to decrease the number and volume of endometriosis implants, suppress inflammation, and increase apoptosis [23]. In vitro studies regarding the relationship between resveratrol and endometriosis are limited. In one randomized trial studying 44 subjects in a university hospital, the effect of resveratrol (40 mg/day) vs. placebo on endometrial pain was assessed. Results concluded that resveratrol did not have a superior effect on endometriosis pain when compared to placebo [23–25].

In vitro studies demonstrate positive effects of resveratrol in reducing invasion of endometriotic stromal cells (ESCs) and suppression of inflammatory response. However, not enough evidence exists to have a solid recommendation for this population.

Antioxidants

One important feature of fruits and vegetables is their natural concentration of antioxidants, including vitamins, minerals, carotenoids, and other phytochemicals. They are abundant in grains, nuts, seeds, fruits, and vegetables [26] and protect cells from the damage caused by free radicals [27]. Free radicals may attack important molecules, resulting in damage, or oxidative stress. Free radicals can come from external sources like smoking or pollutants. They may also come about naturally during normal bodily processes [28]. Antioxidants essentially defend the body from oxidative damage. Recent studies have focused on the role of oxidative stress, which may be implicated in the pathophysiology of endometriosis causing a general inflammatory response in the peritoneal cavity [2].

Antioxidants may be administered either via food sources or by supplementation. In a randomized, placebo-controlled trial, effect of antioxidant vitamins (vitamins E and C) in women with pelvic pain due to endometriosis was assessed. Patients were randomly assigned between two groups: vitamin E (1200 IU) and vitamin C (1000 mg) combination or placebo, daily for 8 weeks before surgery. After treatment with antioxidants, chronic pain ("everyday pain") improved in 43% of patients in antioxidant treatment group as compared to the placebo group ($P = 0.0055$). In the same group, dysmenorrhea ("pain associated with menstruation") and dyspareunia ("pain with intercourse") decreased in 37% and 24% of patients, respectively [29].

Another study was conducted with a different combination of antioxidants—N-acetylcysteine (600 mg), alpha-lipoic acid (200 mg), bromelain (25 mg), and zinc (10 mg)—administered for 6 months. This was a multicentered, open-label, non-comparative study. Within 3 months of treatment, researchers analyzed the outcomes of 373 participants. After 6 months, administration of NSAIDs and antioxidant "cocktails" were shown to have a statistically significant decrease of pain intensity was seen (as measured on the visual analogue scale) (82.7%, $p < 0.05$) [30].

Probiotics

While limited data available on the benefits of probiotics and endometriosis in humans. It has been hypothesized that gut microbiota is not only important for gastrointestinal function but also plays a major role in regulating inflammatory and proliferative conditions as well as having an effect on estrogen metabolism and stem-cell homeostasis. One animal study showed that rhesus monkeys with endometriosis had lower levels of bacteria (lactobacilli) when compared to monkeys without endometriosis [31]. Another study reported that *Lactobacillus gasseri* OLL2809 (given orally) in mice significantly reduced the total weight and surface area of endometrial implants suppressing development [32]. These findings suggest that gut bacteria and the oral supplementation of specific probiotics may play a role in the severity of endometriosis.

Turmeric

Turmeric is a spice that has been used for centuries and contains the polyphenol curcumin which has an anti-inflammatory and antioxidant effect in humans in certain doses [33]. Evidence suggests that administration of curcumin may play a positive role in alleviating symptoms associated with endometriosis, although a standard dose is yet to be established [33, 34].

A systematic assessment of chemokine and cytokine secretion confirmed that many autacoids are differentially expressed by stromal cells derived from the eutopic endometrium of endometriosis subjects, relative to women without the disease. Results indicated that curcumin treatment resulted in normalization of these proteins [35].

Although turmeric is "natural," in certain doses, it has the potential to interact with certain medications. Women with a diagnosis of endometriosis should not supplement with turmeric without her health-care provider's knowledge. Caution for drug-nutrient interaction should be taken if a woman is taking blood thinners, stomach acid reducers, and/or medications that help regulate hyperglycemia.

Omega-3 Fatty Acids

Dietary fats are found in a variety of foods, including red meat, seafood, dairy, nuts, seeds, olives, peanuts, soybeans, and avocados. The fat found in foods is primarily a mixture of triglycerides.

Fatty acids are classified according to the number of carbons in the chain and the number of double bonds between the carbon atoms [36]:

- Polyunsaturated fatty acids (PUFAs) have more than one double bond.

PUFAs are further classified as either omega-3 or omega-6 fatty acids. The most common omega-6 fatty acids are linoleic acid and arachidonic acid. Linoleic acid is found in vegetable oils, while arachidonic acid is found in animal fat, red meat, and dairy products. The omega-3 fatty acids include linolenic acid, found in plant foods and plant leaves, flaxseed, soy, canola, and walnut oils; and EPA and DHA, found in fatty fish and fish oil [36].

In animal models, omega-3 purified fatty acids have shown to reduce risks thought to lead to endometriosis-associated pain, have minimal side effects, and have no effects on fertility [37].

To assess the effect of omega-3 fatty acids and risk of endometriosis, researchers utilized data from the NHS II cohort (mentioned previously). Utilizing a food frequency questionnaire and reported outcomes, total fat consumption was not associated with endometriosis risk. Women in the highest fifth of long-chain omega-3 fatty acid consumption were 22% less likely to be diagnosed with endometriosis compared with those in the lowest fifth of intake (95% CI = 0.62–0.99; $P_{\text{trend}} = 0.03$).

In addition, those in the highest quintile of trans-fat intake were 48% more likely to be diagnosed with endometriosis (95% CI = 1.17–1.88; $P_{trend} = 0.001$) [38].

To determine the relationship between circulating levels of PUFAs and endometriosis in women, a cross-sectional study of serum PUFAs and clinical data from 205 women were assessed. Women with high serum eicosapentaenoic acid (EPA) levels (an omega-3 fatty acid found primarily in certain fish) were 82% less likely to have endometriosis compared to women with low EPA levels (odds ratio (OR) = 0.18, 95% CI = 0.04–0.78) [39]. Dietary sources of EPA fatty acid include salmon, anchovy, tuna, and trout.

The Women's Risk of Endometriosis, a case-control population-based study of 944 women, was conducted to determine whether dietary factors influence risk of developing endometriosis. An inverse correlation was observed between the consumption of the saturated fatty acids, monounsaturated fatty acids, and trans fats and the risk of endometriosis. However, in this case, the control group ate fewer calories, less fat in general, and had lower total cholesterol compared to women with endometriosis [19].

Red Meat

Red meat consumption is associated with increased risk of various health conditions, including colorectal carcinoma, type 2 diabetes, and cardiovascular disease [40]. Few studies have explored the relationship between red meat intake and endometriosis; however, the Women's Risk of Endometriosis Study did not report an increased risk of endometriosis with increasing servings/week of red meat [19].

Parazzini et al. analyzed data collected from two case-controlled studies to determine whether there is a relationship between certain dietary measures and endometriosis. They concluded a considerably higher risk of endometriosis with consumption of ham (OR = 1.8, CI 95%), beef, and other kinds of red meat (OR = 2.0, CI 95%) [13].

Utilizing the NHS II cohort data from 3800 confirmed cases of endometriosis, Yamato et al. found that women who consumed more than two servings of red meat per week had a 56% (95% CI = 1.22–1.99; $P_{trend} < .0001$) higher risk of developing endometriosis compared with women who consumed one or fewer servings of red meat. Intakes of poultry, fish, shellfish, and eggs were unrelated to endometriosis risk [41].

Soy and Phytoestrogens

Soybeans and soy foods have been shown to protect against cancer, osteoporosis, cardiovascular disease, hypertension, stroke, renal disease, and diabetic nephropathy. The amino acids in soybeans are linked to their health benefits [42].

Sources of dietary soy include, but are not limited to:

- Soybeans and edamame
- Tofu
- Miso
- Natto
- Tempeh

Soy foods contain isoflavones. Isoflavones are classified as phytoestrogens and also have nonhormonal effects. Phytoestrogens ("dietary estrogens") are classified as nonsteroidal estrogen and behave differently than classic estrogens [42].

Phytoestrogens are plant-derived polyphenols that structurally and functionally mimic 17β-estradiol which may mimic estrogenic activity and act as "adaptogens" modulating or restoring balance in the body [42–44]. Phytoestrogens can have an estrogenic or antiestrogenic effect depending on plasma concentration of isoflavones and endogenous estrogens, depending on individual characteristics, such as gender and menopausal status [45, 46].

Phytoestrogens include lignans and isoflavonoids [42]. Lignans are found in whole grains, certain seeds, fruits, vegetables, and flaxseed [47, 48].

Due to the connection between endometriosis and estrogen levels, it is possible that consumption of soy or foods containing phytoestrogens in general can be associated with a higher risk of developing endometriosis [20].

In a case-controlled study of 138 Japanese women evaluating the relationship between dietary soy intake and endometriosis, there was a significant correlation in higher level of urine isoflavones in women with stage III or IV endometriosis than the group with stage I or II ($P_{trend} = 0.01$ and 0.06, respectively) [49].

Phytoestrogen intake and symptoms associated with endometriosis have been demonstrated in in vitro studies [50, 51]; future research should look into in vivo studies.

Dairy Products

Many women suffering from endometriosis refrain from ingesting dairy products. Examples of dairy products are milk, cheese, and yogurt. The theory is that eliminating this food group will reduce symptoms of endometriosis and the risk of developing endometriosis. Substantial evidence-based recommendations that align with this theory are lacking.

NHS II cohort assessment of dairy consumption and endometriosis risk revealed intakes of total and low-fat dairy foods were associated with a lower risk of endometriosis. Women consuming more than three servings of total dairy foods per day were 18% less likely to be diagnosed with endometriosis than those reporting two servings per day (rate ratio = 0.82, 95% CI: 0.71, 0.95; $P_{trend} = 0.03$) [52]. A well-designed clinical trial evaluating the relationship of dairy intake and symptoms associated with endometriosis is still needed.

Other Risk Factors

Other risk factors for endometriosis include below average body mass index, smoking, and alcohol use [53]. One study investigating lifestyle factors before endometriosis diagnosis largely found no association between alcohol, caffeine, smoking, and physical activity and risk of endometriosis [54].

A meta-analysis of 15 studies found a negative association between any alcohol consumption and endometriosis risk [55].

A cross-sectional study with a large sample size (28,822 women, with 1228 diagnosed with endometriosis) explored risk factors such as age at menarche, level of education, body mass index (BMI), parity, oral contraceptive (OC) use, infertility, coffee consumption, smoking, and alcohol intake and how they relate to endometriosis. Late age at menarche and higher parity were found to have an inverse association with endometriosis, while alcohol intake did not [56].

In a recent retrospective study conducted at the Royal Women's Hospital and the University of Melbourne, Australia, researchers concluded that while fewer obese women had laparoscopically confirmed endometriosis, those who did had significantly increased disease severity scores (based on the revised American Fertility Society system) [57].

Conflicting results have been published on the role of tobacco smoking and risk of endometriosis. Results of a meta-analysis of available studies indicated there was no correlation between tobacco smoking and the risk of endometriosis. The results were consistent considering ever, former, current, moderate, and heavy smokers' status, across types of endometriosis, and study design [58].

Exposures during childhood and adolescence may have a large impact on endometriosis [59]. In a prospective cohort of 98,995 women, researchers analyzed risk factors in children and adolescents and chances of developing endometriosis. There were inverse relationships of endometriosis risk with menarcheal age ($P_{trend} < 0.0001$) and with menstrual cycle length before 17 years of age ($P_{trend} = 0.06$), whereas menstrual cycle regularity before 17 years of age was not associated with higher risk. There were modest associations of endometriosis risk with exposure to pet animals (OR = 1.12 [95% CI = 1.02–1.22]) or living in a farm for 3 or more consecutive months during childhood (1.12 [95% CI = 1.02–1.24]), although with no link to any specific type of farm animal.

Passive (secondhand) smoking exposure was shown to be positively related to endometriosis risk later in life [59].

There is always room for improvement and growth; avenues for future research include long-term impact of endometriosis on other chronic conditions, for example, cardiovascular health. While there are still gaps in research surrounding diet and different foods, another line of investigation could be invstigating the link between endometriosis and female metabolism and how the female body breaks down and absorbs vitamins and nutrients.

Eating disorders frequently begin during teenage years and affect 3.8% of adolescent girls [60]. To date, there are no studies available investigating the relationship of

eating disorders and endometriosis. In 2014, Riazi et al. published a qualitative study in which a patient reported avulsion or inability to eat while experiencing endometriosis-related symptoms [61]. Do endometriosis-related symptoms play a role in a teenager's eating disorder development or how teens perceive food? What is the prevalence of endometriosis in teenagers struggling with eating disorders such as anorexia nervosa and bulimia nervosa?

Dietary and lifestyle modifications are easy, inexpensive, and natural measures women can take to reduce their risk of developing endometriosis and alleviate symptoms. Despite existing and promising evidence, research in this specific area is severely lacking. To further add to the challenge of providing firm recommendations for nutrition interventions, the studies that do exist regarding this relationship sometimes provide conflicting results. Thus, making definitive diet and lifestyle recommendations regarding endometriosis is challenging but provides many opportunities for future research.

Conclusion

The risk of developing endometriosis as well as symptoms associated with endometriosis has been shown to have an inverse relationship with certain nutrition or lifestyle factors. The NHS II cohort has provided a large sample size spanning over 4 years which allows for a better understanding of certain nutrition measures and how they relate to endometriosis risk. Intake of citrus fruit, foods rich in beta-cryptoxanthin, omega-3 fatty acids, and dairy foods was shown to reduce the risk of developing endometriosis, while intake of refined sugar, simple carbohydrates, and red meat was shown to increase the risk.

Flo Living provides a comprehensive and easy to follow list of 10 health eating tips to keep in mind at the grocery store [62]:

1. Add probiotics to your diet to maintain healthy gut bacteria.
2. Fiber is key; go for leafy greens, fruits, and other fiber-filled foods which will also aid in a healthy gut.
3. Healthy fats are your friends; olive or coconut oil and avocados will help hormone balance.
4. Decrease inflammation by preparing lean animal proteins.
5. Kale, broccoli, cabbage, beets, artichokes, lemons, onions, garlic, and leeks are immune response enhancers and should make more of an appearance on your plate.
6. Drink teas high in milk thistle, flaxseeds, and dandelion root (all liver detoxifiers) to boost estrogen metabolism.
7. Primrose oil has been shown to inhibit tumor growth and decrease inflammation.
8. Dairy, wheat, alcohol, and caffeine should make rare appearances in order to improve immune response.

9. To balance out excess estrogen, include daily supplements of vitex and B6 into your routine.
10. Toxic forms of estrogen can be found in everything today; if possible, always choose organic options free of pesticides, and check the labels on your household cleaners, cosmetics, and bathroom products.

Although currently, strong evidence regarding certain nutrients does not exist, eating a well-balanced diet containing fruit, complex carbohydrates, meat low in trans-fat, rich omega-3 fatty acids and with moderate alcohol consumption will not have a detrimental effect on women's health regardless of endometriosis diagnosis or risk.

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Chapter 39
Medical Management of Endometriosis in Adolescents

Gisselle Perez-Milicua

Abbreviations

ACOG	American College of Obstetrician and Gynecologists
AI	Aromatase inhibitors
BMD	Bone mineral density
CEE	Conjugated equine estrogen
CHT	Combination hormonal therapy
COC	Combined oral contraceptive
DEXA	Dual-energy X-ray absorptiometry
DMPA	Depot medroxyprogesterone acetate
ENG	Etonogestrel
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
LH	Luteinizing hormone
LNG-IUD	Levonorgestrel-releasing IUD
MPA	Medroxyprogesterone acetate
NA	Norethindrone acetate
NSAIDs	Non-steroidal anti-inflammatory drugs
SERM	Selective estrogen receptor modulators
SPRM	Selective progesterone receptor modulators
TENS	Transcutaneous electrical stimulation
WHO	World Health Organization

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Introduction

Endometriosis in adolescents, like in adults, is considered a chronic disease without a cure. It is also considered a progressive disease which can continue to advance if left untreated [1]. The medical management of endometriosis has significantly evolved since ancient times and the microscopic unveiling of endometriosis in 1860 by Carl von Rokitansky. Over the past few centuries, significant advances in medical science and technology have transformed how endometriosis is now treated in modern times. The goals of medical management in adolescents in the present era include adequate pain control and hormonal suppression to avoid progression of the disease and to protect the adolescent's fertility in the future [2]. Diagnostic laparoscopy is commonly utilized in the evaluation of suspected endometriosis. At the time of initial laparoscopy, conservative surgical therapy with resection, coagulation, or ablation of endometriotic lesions is recommended [3]. Following surgery, hormonal suppressive therapy is the first-line therapy for adolescents which can be initiated post-operatively or continued if previously started in cases of suspected endometriosis [2]. There is no single best therapy for the medical management of endometriosis, and multiple treatment modalities are usually necessary.

History of Medicine in the Treatment of Endometriosis

Endometriosis is a painful, uterine condition that has affected women of reproductive age throughout history and all over the world. The scientific knowledge of symptoms, pathophysiology, and treatment for endometriosis has gradually unfolded over time.

Ancient Times

The oldest known possible record representing a case of endometriosis was found in the thirteenth-century medical manuscript known as MS Ashmole 399 (folios 33–34). In this manuscript, a drawing depicts a woman doubled over in pain most likely suffering from dysmenorrhea or endometriosis which at the time was known as "strangulation or suffocation of the womb." Ancient Egyptians, the Hippocratic Corpus, the Greek philosopher Plato, Roman scholar Celsus, Greek physician Pedanius Dioscorides, and physician Claudius Galen of Pergamon, among others, were instrumental in identifying possible symptoms and treatments for endometriosis in ancient times.

Ancient medical therapies, however, were limited. Most therapeutic options for endometriosis involved vaginal suppositories, ingestible preparations, fumigants, and medicinal herbs such as *Prunella vulgaris*. The suppositories would contain a

variety of different substances such as urine from men or bulls, pomegranates, pine tar water, chaste tree (*Vitex agnus-castus*), castor oil, or cantharides which were dried blister beetle remains. Although studies are limited on the pharmacological effects of these substances, they may exert anti-estrogenic, anti-proliferative, or anti-inflammatory properties which are some of the key features of the treatment of endometriosis in the modern age [4].

The Middle Ages

The Middle or Dark Ages, from the fifth through fifteenth century, are considered a period of stagnation in the scientific and cultural worlds. An obsession with supernatural forces overpowered science and medicine. Symptoms of endometriosis were still attributed to "uterine suffocation" or hysterical convulsions which may have been mistaken for witchcraft or demonic possession. Women were therefore subjected to harsh and cruel "treatments" including torture, executions, exile, exorcisms, choking, and "shouting therapy."

Medieval physicians, however, were active in their search for a treatable cause of endometriosis symptoms. For example, the concept of painful uterine contractions was first introduced by Aëtius of Amida during this time period. Outside of Europe, Asian countries and Muslim medicine were flourishing as progressive centers for medicine and science leading to the discovery of new medicines such as colchicum, senna, camphor, nutmeg, cloves, and alcohol mixtures. These treatments have become essential medicines even after the Middle Ages. The Trotulan text, published in the twelfth century by female physician Trotula, suggests injecting powdered goat or fox testicles into the vagina with a suppository. Vaginal suppositories of ground gonads are not used in the modern age but are similar to the treatments described in ancient Hippocratic texts [4].

The Sixteenth to Eighteenth Centuries

During this time period, medical treatment was at a crossroads between the old and new worlds of science. Women's health took a few steps backward as gynecologic disorders became considered psychological in nature or stemming from immorality. However, several exceptional advancements leading to our modern understanding of endometriosis were made primarily from organized medical education and autopsies, such as the refluxed blood theory and hereditary disposition. Medical treatment for endometriosis did not advance significantly during these centuries. Pregnancy was still considered a means to prevent or cure endometriosis; a "hysterical pill" containing opium was at times recommended for cyclical pain; and previous treatment options also continued to be used [4].

The Nineteenth to Twentieth Centuries

Medical science and technology experienced impressive growth and development during the nineteenth and twentieth centuries in the understanding of human disease and medical management, particularly in women's gynecology. Non-surgical treatments for mild cases of endometriosis were popular before anesthesia such as morphine, opium, alcohol, hot douches, and medical marijuana. Other treatments consisted of purging emetics and enemas or ingestion of questionable concoctions, i.e., Pinkham's Vegetable Compound and Hoffmann's soothing liquor, which consisted of mostly ether. Invasive medical treatment options involved leeches at the cervix which could be lost in the vagina or uterus, caustic substances applied in the uterine cavity or genital tract, cervical dilator sponges or intrauterine devices which in most cases led to uterine infections, and manual adjustment of the uterus. The most invasive techniques were surgical procedures which were quite literal in their names such as the "twist and tear off," "tapping," or "clawing out" methods, electrocautery, dilation and curettage, hysterectomy, oophorectomy, and partial excisions. In the twentieth century, the introduction of the hormonal contraceptive pill and video-assisted laparoscopy catapulted the treatment of endometriosis into the modern age [4].

Hormonal Suppressive Therapy

In the modern age, the first-line treatment option for adolescents with surgically proven endometriosis or with suspected endometriosis is hormonal suppressive therapy [2]. Hormonal suppressive therapy aims to regulate the hormonally responsive ectopic endometriotic lesions which are characteristic of endometriosis. Suppression of ovarian estradiol production decreases the hormonal stimulation for endometriotic growth and proliferation while also inducing atrophy of the endometriotic lesions [5]. Synthetic progestins also induce atrophy through their androgenic effects [6]. The decreased hormonal stimulation and atrophy of the endometriotic lesions results in a reduction in pain symptoms associated with endometriosis.

Although hormonal therapy can be effective in controlling endometriosis-associated pain, there is controversy in the adolescent literature as to whether hormonal suppressive therapy can prevent recurrence or disease progression [7]. A small case series showed that adolescents with laparoscopy-proven endometriosis who were non-compliant with medical management had progression of disease on repeat laparoscopy [8]. A retrospective study in adolescents and young adults showed that combined surgical and medical management impedes disease progression [1]. In this study, patients received hormonal suppression after initial laparoscopy, and on repeat laparoscopy, 70% of patients had no change in stage of the disease, 19% improved by one stage, 1% improved by two stages, and 10%

worsened by one stage [1]. In another retrospective study, 74% of adolescents had recurrent or persistent symptoms, 36.8% had recurrent endometriomas, and 50% had recurrent deep infiltrating endometriosis despite hormonal therapy [9]. Additional studies are needed in the adolescent population to better evaluate the efficacy of medical therapy in the prevention of disease progression and recurrence. Hormonal suppressive therapy should continue to be offered to adolescents with endometriosis as it is effective in treating pain symptoms. Moreover, discontinuation of hormonal suppressive therapy is associated with a high recurrence rate of endometriosis-associated pain [10]. Therapy should therefore continue until the patient is ready to become pregnant [2].

Selection of Hormonal Suppressive Therapy

In the treatment of endometriosis, there is no single best therapy for hormonal suppression. Several factors should be taken into consideration before selecting a medical therapy in the adolescent population. Treatment options should be reviewed thoroughly with each patient, and her active participation in the decision-making process should be encouraged. Therapy can then be selected based on patient's preferred choice, likelihood of compliance with selected choice, need for effective contraception in sexually active adolescents, and any known contraindications to hormonal methods. Adolescents must be reminded that trials of different types of hormonal suppressive therapy may be necessary in order to optimize pain control.

Combination Hormonal Therapy

Combination hormonal therapy (CHT) refers to the hormonal methods that contain both estrogen and progestin. CHT includes combined oral contraceptives (COCs), the contraceptive patch, and the contraceptive vaginal ring. CHT is an effective therapy due to its hormonal influence on endometriotic lesions and subsequent decrease in prostaglandin release. For primary dysmenorrhea, cyclic CHT is considered an effective treatment option. A randomized controlled trial comparing adolescents taking cyclic COCs versus placebo showed that COCs users had significantly less dysmenorrhea and required less pain medication than placebo users [11].

For the treatment of endometriosis, however, CHT is recommended to be administered on a continuous basis to achieve a "pseudopregnancy" state as initially described by Kistner [12]. The administration of continuous CHT results in inactive endometriotic lesions and amenorrhea due to the hormonal effects caused by the estrogen and progestin combination [12]. Continuous COCs were found to provide significant pain reduction from baseline in a prospective study of adult women with dysmenorrhea due to endometriosis [13]. For menstrual suppression, the triphasic COCs are not effective due to the hormonal fluctuations found in their formulation

doses. To achieve menstrual suppression, monophasic COCs are preferred over triphasics. In addition to COCs, the transdermal patch and the vaginal ring can also be used on a continuous basis for the treatment of endometriosis. In an observational comparative trial, treatments with continuous vaginal ring and continuous transdermal patch resulted in improvement from baseline scores for dysmenorrhea, dyspareunia, and non-menstrual pelvic pain [14].

Adolescents should be made aware of potential side effects associated with continuous CHT. Side effects from continuous CHT can include irregular bleeding, headaches, nausea, fluid retention, emotional lability, and hypertension. Adolescents and their parents should be reassured that most patients on CHT have no significant harmful effects. If COCs are selected as the patient's desired choice, the adolescent patient should be encouraged to use an alarm on their personal cell phone as a reminder to take the pill every day at the exact same time. A lack of compliance will often result in breakthrough bleeding. Alarms are also encouraged as a reminder to change the contraceptive patch or the vaginal ring at the appropriate times. Electronic or paper menstrual calendars, in case of breakthrough bleeding, may also be helpful to track their bleeding and compliance with the medication. Adolescents should be counseled on the importance of compliance, and providing them with educational resources may facilitate their understanding of the treatment plan.

Progestin-Only Therapy

Progestin-only therapy offers an alternative to patients who have contraindications to estrogen-containing therapy, for those patients who have failed CHT, or for those patients that desire additional treatment options. Synthetic progestins work by inhibiting the growth of endometrial tissue and exerting progestogenic antimitotic activity in endometriotic lesions [6]. The ensuing decidualization and atrophy of endometriotic lesions result in an improvement in pain symptoms of endometriosis. Different types of progesterone-only therapy vary in effectiveness and side effects which should be reviewed with each patient. Progestin-only therapy includes norethindrone acetate (NA), oral medroxyprogesterone acetate (MPA), depot medroxyprogesterone acetate (DMPA) in a subcutaneous and an intramuscular formulation, the 52 mg levonorgestrel-releasing intrauterine device (LNG-IUD), and the etonogestrel (ENG)-releasing contraceptive implant. NA and the subcutaneous DMPA are the only members in this class of progestin-only therapy that have been approved by the US Food and Drug Administration (FDA) for the treatment of pain due to endometriosis [15].

Norethindrone Acetate NA is frequently used as a method of menstrual suppression in the adolescent population; however, data is limited in the use of NA for the treatment of endometriosis in adolescents [16]. A retrospective study of 194 adolescents and young adults with histologically confirmed endometriosis showed that NA as a single-agent therapy improved endometriosis-related pain in 65% of the

patients across all stages of endometriosis [17]. Several studies in the adult population have proven the benefits of NA in the treatment of symptomatic endometriosis [18]. NA is the only oral progestin currently approved to treat endometriosis, and the FDA label recommends a starting dose of 5 mg/day orally for 2 weeks followed by increments of 2.5 mg/day every 2 weeks to reach 15 mg of NA per day [15]. NA is comparatively affordable, and it does not have deleterious effects on bone density or on serum lipids as other treatment options [17]. NA is partially converted into estrogen with subsequent positive effects on bone metabolism [19]. The most common side effects of NA are breakthrough bleeding and weight gain [18]. Other reported side effects in adolescents include acne, mood liability, vasomotor instability, depression, hair loss, headaches, and nausea [17].

Medroxyprogesterone Acetate Oral MPA has been studied in adult women for the treatment of endometriosis. A study in 21 symptomatic women with endometriosis showed that 80% of the patients had an improvement of symptoms, pelvic nodularity, and tenderness when using MPA 50 mg on a daily basis [20]. Studies evaluating the effectiveness of oral MPA in the adolescent population are lacking. DMPA is a highly effective contraceptive method that has also been used to treat symptomatic endometriosis [18]. DMPA comes in two formulations: 104 mg for subcutaneous injection or 150 mg for intramuscular administration. Both formulations are given at an interval of every 3 months. When compared to leuprolide acetate, subcutaneous DMPA was found to be statistically equivalent in reduction in pain symptoms after 12 months with significantly less side effects [21, 22].

The prolonged use of DMPA is associated with a decrease in bone mass or bone mineral density (BMD), and the greatest bone loss occurs over the first 2 years of treatment, after which the BMD levels are stabilized [18]. The concerns over the effect of DMPA on BMD prompted the FDA to issue a black box warning in 2004. The FDA warning reports that significant BMD loss is possible, the loss of BMD may be greater with increased duration of use, the loss may not be completely reversible, and it is unknown if use during adolescence or early adulthood will decrease peak bone mass and increase future osteoporotic fracture risk. In addition, it recommends to only use DMPA for more than 2 years if other hormonal methods are inadequate. Additional studies are needed to evaluate the long-term effects of DMPA on BMD and fracture risk. The American College of Obstetrician and Gynecologists (ACOG) and the World Health Organization (WHO) both support the use of DMPA without restrictions on age or on duration of therapy as the advantages of using DMPA generally outweigh the risks [22]. Healthcare providers should review the FDA warnings with each patient, and adolescents should be counseled about other hormonal options without effects on BMD [23].

Levonorgestrel-Releasing Intrauterine Device The 52 mg LNG-IUD releases 20 μg/day of levonorgestrel into the cavity of the uterus over a course of 5 years. The hormonal effect on the local and ectopic endometrial tissue includes endometrial glandular atrophy, decidualization, decreased endometrial proliferation, and increased apoptosis [24]. The LNG-IUD has been used in the treatment of

endometriosis in adult women, and multiple randomized controlled trials have demonstrated its effectiveness in reducing pain related to endometriosis [18]. The use of LNG-IUD showed comparable effectiveness when compared to gonadotropin-releasing hormone (GnRH) analog and DMPA [25, 26]. When compared to expectant management, the LNG-IUD was demonstrated to be superior [27]. Data on the effectiveness of LNG-IUD in the treatment of symptomatic endometriosis in the adolescent population is limited. A small retrospective chart review of adolescent patients showed that LNG-IUD users had better pain control and reported an improved quality of life compared to non-users [28]. Some authors have recommended the placement of a LNG-IUD in adolescents at the time of diagnostic laparoscopy for chronic pelvic pain [29]. Multiple studies have shown that even if endometriosis is not visualized during laparoscopy, the LNG-IUD may still help improve dysmenorrhea and chronic pelvic pain. Placement of a LNG-IUD in the operating room at the time of laparoscopy may also avoid potential anxiety with an in-office procedure [30]. The use of LNG-IUD in the adolescent population should be encouraged for the treatment of multiple medical conditions including endometriosis.

Etonogestrel Implant The ENG-releasing implant is a contraceptive device which contains 68 mg of ENG, and it is placed subdermally in the upper arm. The implant is currently approved by the FDA for contraception and for the duration of 3 years; however, recent data suggests it may last longer [31]. Data evaluating the effectiveness of the ENG implant in the treatment of endometriosis is limited and only available in case reports and case series in adult women [18]. Additional studies are needed before a recommendation can be made regarding the use of the ENG implant for the treatment of endometriosis in adolescents.

Gonadotropin-Releasing Hormone Agonists

As mentioned earlier, the first-line therapy for the medical management of endometriosis in adolescents is hormonal suppressive therapy with either continuous CHT or progesterone-only therapy. Patients who fail the first-line therapy may benefit from a GnRH agonist with add-back therapy for at least 6 months [2]. GnRH agonists are not superior to COCs or other medical treatments for endometriosis [32, 33]; however, they are very effective at reducing or eliminating endometriosis-related pain [34, 35]. Initially, GnRH agonists produce an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which results in a transient increase in estrogen. This stimulatory phase, also known as the flare effect, results in a withdrawal bleed at approximately 14–21 days after initiation of the GnRH agonist. Symptoms of pain and bleeding may temporarily worsen during this phase. Continuous GnRH stimulation will then lead to decreased levels of LH and FSH by downregulation of the pituitary gland with subsequent ovarian suppression and decreased estrogen levels. The outcome of GnRH agonist therapy is a reversible

induction of a hypogonadotropic, hypoestrogenic state which has been demonstrated to be successful in the treatment of endometriosis.

GnRH agonists are available in different formulations and all appear to be efficacious [15]. These formulations include leuprolide acetate (intramuscular injection 11.25 mg every 3 months or 3.75 mg every 4 weeks), goserelin acetate (subcutaneous injection 3.6 mg every 28 days), and nafarelin acetate (nasal spray one puff in one nostril twice daily, alternating nostrils). Leuprolide acetate is the most commonly used GnRH agonist approved for the treatment of endometriosis in the United States. In adolescents, compliance is an issue; therefore, intramuscular dosing is more commonly the preferred formulation.

GnRH agonist therapy is associated with significant side effects, and these must be carefully considered in all patients, particularly in the adolescent population. Side effects can include decreased bone density, hot flashes, headaches, vaginal dryness, difficulty sleeping, depression, and mood swings [3]. The decrease in bone density is of significant concern in adolescents as acquisition of bone density continues after puberty and throughout the adolescent years. Peak bone mass is attained during the second decade of life, and up to 40–60% of adult bone mass is accrued during adolescence [36]. Due to these side effects, healthcare providers and adolescents may not be willing to start GnRH agonist therapy for the treatment of endometriosis.

Add-back therapy has been demonstrated in multiple studies in adults to be helpful in treating the associated side effects from GnRH agonists. This therapy refers to the administration of low doses of hormones throughout the duration of treatment with a GnRH agonist. Add-back therapy is based on the "estrogen threshold hypothesis" which proposes that a low level of estrogen concentration (30–45 pg/mL) is best to prevent bone loss without stimulating endometrial growth and exacerbating endometriosis [37]. The addition of add-back therapy has been demonstrated to effectively reduce or eliminate the bone mineral loss that is seen with GnRH agonist therapy [38, 39]. It also provides symptomatic relief and prevention of vasomotor symptoms from a hypoestrogenic state while maintaining the efficacy of the GnRH agonist in reducing pelvic pain [38].

Multiple options for "add-back therapy" have been studied in adults including progestin alone, estrogens in combination with a progestin, and progestin and bisphosphonates. NA (5 mg/day) has been approved by the FDA for the treatment of endometriosis as add-back therapy. Data is limited in adolescents; however, recent studies on add-back therapy show promising results as in the adult population. A retrospective study showed that BMD was normal in most adolescents with endometriosis who received a GnRH agonist and add-back therapy with NA (5 mg/day) [40]. Although not FDA-approved, the combination of an estrogen and progestin as add-back therapy has been demonstrated to be effective in reducing pelvic pain and reducing side effects of GnRH agonist therapy in numerous trials in adults. A randomized controlled trial in adolescents and young women from 2015 showed that the total bone mineral content, BMD, and lean mass increased after 12 months of GnRH therapy in the group taking NA (5 mg/day) plus conjugated equine estrogens (CEE) (0.625 mg/day) versus the group receiving NA and placebo [38]. In

regard to quality of life, a trial in 2017 showed that adolescents who received add-back therapy with CEE (0.625 mg) and NA (5 mg/day) were superior to NA alone [41]. Add-back therapy should begin at the initiation of GnRH agonist therapy to preserve bone health and to avoid vasomotor symptoms [2].

Throughout the duration of therapy with a GnRH agonist, patients should be encouraged to increase dietary intake of calcium- and vitamin D-containing foods and beverages to optimize bone health. Examples of calcium- and vitamin D-enriched products include milk, yogurt, cheese, salmon, sardines, tuna, cooked spinach, orange juice, and calcium-fortified cereals [36]. Weight-bearing exercises should also be encouraged such as walking, jumping, running, and dancing.

Treatment with a GnRH agonist has been approved by the FDA for 12 months as the safety of extended therapy has not been extensively evaluated. A few studies in adults have reported treatment beyond 12 months of GnRH agonist with add-back therapy [42]. In adolescents, data on long-term effects is limited. Dual-energy X-ray absorptiometry (DEXA) scanning is not necessary before, during, or after treatment with a GnRH agonist if treated for less than 12 months [2]. Some authors have recommended obtaining a DEXA scan in adolescents after completing 9 months of GnRH agonist therapy and discontinuation of the GnRH agonist if the DEXA scan shows evidence of decreased bone density [3]. If the bone density is normal, the patient can continue with the GnRH agonist and add-back therapy with a DEXA scan repeated at 6 months and, if stable, repeated every 2 years [3]. There are reports of adolescents receiving prolonged GnRH agonist with add-back therapy for the treatment of refractory disease [3]. There is limited data on the long-term effects of GnRH agonist therapy in adolescents, and additional studies are necessary.

At the conclusion of the GnRH agonist therapy, continuous hormonal suppression should be initiated. If treatment with GnRH agonists is not successful at improving pain, repeat diagnostic laparoscopy should be considered as recurrent endometriosis or pelvic adhesions may have developed. Other causes of chronic pelvic pain should also be considered and explored.

Additional Hormonal Suppressive Therapies

Danazol Danazol is an isoxazole derivative of 17-alpha-ethinyltestosterone (ethisterone), and it was the first drug approved by the FDA for the treatment of endometriosis. It inhibits the release of gonadotropins resulting in anovulation, menstrual suppression, and prevention of growth of the endometriotic implants. A Cochrane review from 2007 showed that danazol was effective in treating pain associated with endometriosis compared to placebo [43]. Danazol is associated with significant side effects due to its androgenic properties. Side effects include weight gain, edema, acne, oily skin, abnormal bleeding pattern, sweating, deepening of voice, and hirsutism. Some side effects are irreversible such as voice deepening [43]. Due to these

androgenic and undesirable side effects, danazol is not prescribed in the adolescent population.

Dienogest Dienogest is an oral progestin that is used as monotherapy in the treatment of endometriosis-associated pain. It is a fourth-generation progestin that is highly selective for the progesterone receptor, and it exhibits limited androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity with minimal impact on metabolic parameters [44]. This medication is approved for use in the European Union and in Japan. In the United States, dienogest is available in combination with estradiol valerate as a four-phasic combination oral contraceptive pill which is FDA-approved for pregnancy prevention [45]. In adults, dienogest at 2 mg/day was found to be as effective at treating endometriosis-related pain as leuprolide acetate [46, 47]. The estradiol levels are moderately suppressed with dienogest therapy, and a randomized controlled trial comparing dienogest and leuprolide acetate found that mean lumbar BMD was unchanged in the dienogest group, but was decreased in the leuprolide group [46]. Studies in adolescents are limited. A recent study in adolescents showed that dienogest 2 mg/day for 52 weeks was associated with a substantial reduction in endometriosis-associated pain, although a decrease in lumbar BMD was observed with partial recovery after discontinuation of therapy [48]. This study recommends individualized treatment considering the adolescent's risk factors for osteoporosis [48].

GnRH Antagonists GnRH antagonists bind to the same receptors as GnRH agonists, but they have an immediate suppression of gonadotropins without the initial stimulatory phase. Studies have demonstrated a decrease in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia. The FDA recently approved the GnRH antagonist elagolix as the first drug specifically developed for the treatment of moderate to severe pain from endometriosis. The safety and efficacy of elagolix was evaluated in a phase 2 randomized controlled trial which showed that the elagolix treatment groups (150 mg/day and 200 mg/day) had a significantly larger decrease in dysmenorrhea and an even larger decrease in non-menstrual pelvic pain when compared to placebo [49]. Minimal BMD changes were observed with elagolix [49]. Additional studies in the adolescent population are necessary to determine if the results from adult women can be reproducible in adolescents.

Pain Management

Hormonal suppressive therapy has been shown to be effective in treating endometriosis-associated pain symptoms. Patients who have persistent pain despite hormonal suppression may benefit from additional pain management options. Using a combination of medical therapies can help to optimize pain control in endometriosis (Table 39.1).

Table 39.1 Therapy options in the medical management of endometriosis in adolescents

Therapy	Dose	Mechanism of action	Side effects	Use in adolescents
Combination HT (COCs, transdermal patch, vaginal ring)	Varies by method – continuous	1. Suppresses LH and FSH 2. Inhibits ovulation 3. Alters cervical mucus and endometrium	Irregular bleeding, headaches, nausea, VTEs, hypertension, fluid retention, emotional lability	Yes
Norethindrone acetate	5 mg/day PO. Max 15 mg/day	1. Inhibits pituitary gonadotropin release 2. Transforms proliferative into secretory endometrium 3. Alters cervical mucus	Irregular bleeding, weight gain, acne, depression, headaches, nausea, breast pain	Yes
Medroxyprogesterone acetate (PO, IM, SC)	30–50 mg/day PO. 150 mg IM or 104 mg SC every 12 weeks	1. Inhibits pituitary gonadotropin release 2. Transforms proliferative into secretory endometrium 3. Prevents ovulation	Irregular bleeding, amenorrhea, weight gain, acne, decreased BMD, breast pain	Yes
Levonorgestrel-releasing intrauterine device (52 mg)	20 μg/day	1. Local endometrial effects: stromal pseudodecidualization and glandular atrophy 2. Thickens cervical mucus 3. Inhibits sperm capacitation or survival	Irregular bleeding, amenorrhea, abdominal or pelvic pain, acne, vaginitis, ectopic pregnancy	Yes
Etonogestrel-releasing implant (68 mg)	70 mcg/day	1. Inhibits pituitary gonadotropin release 2. Inhibits ovulation 3. Alters cervical mucus and endometrium	Irregular bleeding, amenorrhea, headache, acne, breast pain, depression, nausea	Yes[a]
GnRH agonist (leuprolide acetate)	11.25 mg q12 weeks	1. Analog to GnRH receptors 2. Inhibits gonadotropin release 3. Suppresses ovarian steroidogenesis	Decreased BMD, vasomotor symptoms, decreased libido, depression, flare effect	Yes
Danazol	100–200 mg PO BID x3–9 months	1. Suppresses LH and FSH 2. Weak androgenic activity	Weight gain, edema, acne, oily skin, abnormal bleeding pattern, sweating, deepening of voice, and hirsutism	No

Table 39.1 (continued)

Therapy	Dose	Mechanism of action	Side effects	Use in adolescents
Dienogest	2 mg/day PO	1. Inhibits pituitary gonadotropin release 2. Transforms proliferative into secretory endometrium 3. Prevents ovulation	Irregular bleeding, amenorrhea, weight gain, acne, decreased BMD, breast pain	N/a[b]
GnRH antagonist (elagolix)	150 mg/day	1. Antagonizes GnRH receptors 2. Suppresses LH and FSH release 3. Reduces estradiol and progesterone levels	Irregular bleeding, headaches, nausea, transaminitis, anaphylactic reaction	?[a]
NSAIDs (ibuprofen, naproxen)	Varies	1. Inhibits cyclooxygenase 2. Reduces prostaglandin and thromboxane synthesis	Dyspepsia, nausea, abdominal pain, GI ulcer/bleeding, thrombocytopenia, nephrotoxicity	Yes

HT hormonal therapy, *COCs* combination oral contraceptives, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *VTEs* venous thromboembolism, *BMD* bone mineral density, *GnRH* gonadotropin-releasing hormone, *NSAIDs* non-steroidal anti-inflammatory drugs, *GI* gastrointestinal, *PO* by mouth, *IM* intramuscular, *SC* subcutaneous, *BID* twice daily

[a]Additional studies are needed to establish efficacy in the treatment of endometriosis in adolescents

[b]Not available in the United States as a single agent

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are traditionally the first line of treatment for primary dysmenorrhea. NSAIDs are also commonly used for pain control in patients diagnosed with endometriosis. There is limited evidence evaluating the effectiveness of NSAIDs in the treatment for pain caused by endometriosis in the adolescent population. In a study on 20 adult women with endometriosis, the use of naproxen sodium significantly improved pain compared to placebo [50]. A Cochrane review from 2017, which included the above study, reported that the evidence is inconclusive to show whether or not NSAIDs are effective in managing pain due to endometriosis [51]. The same Cochrane review reported a lack of evidence to determine if an individual NSAID is more effective than another [51]. For the treatment of primary dysmenorrhea, a Cochrane review from 2015 showed that NSAIDs are a very effective treatment compared to placebo [52]. Prostaglandins are likely implicated in the development of pain associated with primary dysmenorrhea and endometriosis. NSAIDs inhibit the enzyme cyclooxygenase, thereby reducing prostaglandin synthesis which results in a reduction of pain. The most widely studied NSAIDs are ibuprofen and naproxen. NSAIDs are a reasonable option as an

adjuvant therapy for pain management in endometriosis and should be the main therapy for pain relief in adolescents [2]. Patients should be made aware of unintended side effects associated with NSAIDs, and patients with contraindications to NSAIDs should avoid them.

Other Pain Management Options

Endometriosis can result in chronic pelvic pain which is oftentimes debilitating and difficult to treat. Evidence supports a multidisciplinary approach to the treatment of chronic pelvic pain [53]. A multidisciplinary team can include a gynecologist, pain management specialist, physical therapist, psychologist, and nutritionist, among other experts. It is not recommended to prescribe narcotics to adolescents to prevent narcotic abuse, dependence, and addiction. Narcotics, however, can be prescribed as a last resort if the patient's pain has not responded favorably to other forms of pain management. Table 39.2 provides an overview of narcotics in endometriosis treatments [55]. If on narcotics, close monitoring is recommended, and early identification and treatment of drug abuse are necessary to prevent the development of addiction. Signs and symptoms of opioid abuse include constipation, nausea, euphoria, slowed respiratory rate, drowsiness, confusion, poor coordination, need for increased dose, and hyperalgesia [56]. Alternatively, antidepressants and anticonvulsants are frequently used for treating chronic pelvic pain; however, there is limited data on efficacy [57].

Table 39.2 Narcotics for the treatment of endometriosis-related pain and associated side effects [54, 55]

Hydrocodone with acetaminophen	Norco	5 mg/325 mg
	Vicodin	7.5 mg/325 mg
	Lortab	10 mg/325 mg
Oxycodone with acetaminophen	Percocet	5 mg/325 mg, 7.5 mg/325 mg, 10 mg/325 mg, 10 mg/500 mg
Oxycodone	5 mg, 10 mg, or higher ***not recommended for long-term maintenance therapy	
Tylenol with codeine	T#3 T#4	
Side effects of narcotics Fatigue, drowsiness Itchiness Shortness of breath Dizziness, poor coordination Irritability Nausea Confusion	Anxiety Changes in appetite-hunger or insatiety Headache Hallucinations Dependency Constipation Feeling of euphoria (high)	

***Narcotics only to be used in refractory cases and as part of a multi-disciplinary treatment approach in consultation with a pain medicine specialist. Narcotics are not recommended for long-term maintenance therapy

Other integral components of a multidisciplinary approach to chronic pelvic pain management include cognitive and behavioral techniques such as guided imagery, progressive muscle relaxation, biofeedback, and self-hypnosis [57]. Musculoskeletal conditions may also contribute to the chronic pelvic pain from endometriosis. Adolescents with musculoskeletal etiologies respond well to physical therapy, and this strategy may also be helpful in treating chronic pelvic pain [58]. Transcutaneous electrical stimulation (TENS) is a widely used adjuvant to chronic pain therapy, but additional trials are needed to evaluate efficacy [57]. Herbal therapy, acupuncture, dietary supplements, and other alternative medicine treatment options are also available for the treatment of chronic pelvic pain with endometriosis [57, 59].

Refractory Pain

Optimizing pain control in the treatment of endometriosis in adolescents is crucial. Adolescents have a high risk of non-compliance if they experience unfavorable side effects with a medical therapy or if their pain is not well controlled. It is important to schedule adolescents for frequent visits in the office to ensure compliance and to regularly review their symptoms and concerns. If pain is persistent despite hormonal suppressive therapy and pain medications, a careful evaluation must follow. The differential diagnosis of chronic pelvic pain is extensive, and other possible causes of chronic pelvic pain should be investigated. The adolescent may also need a repeat laparoscopy to evaluate for recurrent endometriosis or pelvic adhesions that may have developed throughout the course of the treatment. Surgical treatment in adolescents should be conservative with the goal to resect and destroy all visible lesions and removal of endometriomas if present. Additional surgical options for persistent pain are not recommended in adolescents. Therapy with a GnRH agonist with add-back therapy may be beneficial for long-term treatment of refractory pain from endometriosis in adolescents; however, additional studies are needed to evaluate safety and efficacy. A multidisciplinary approach is recommended for the treatment of chronic pelvic pain from endometriosis often with a pain management specialist. Complementary and alternative therapies should also be explored. Providing constant support and education to adolescents is key. Adolescents may also find support groups to be helpful, and they should also be encouraged to join community groups and electronic social networks on endometriosis.

Future Treatment Options

Selective estrogen receptor modulators (SERM), selective progesterone receptor modulators (SPRM), progesterone antagonists, aromatase inhibitors (AI), statins, angiogenic inhibitors, and botanicals are being evaluated as potential treatment options for endometriosis [5]. AIs are a promising treatment option for

endometriosis-associated pain in the adult population [60]. They act directly on endometriotic deposits which have higher levels of aromatase expression compared to normal endometrium. In a systematic review, adult women who received AI therapy had a significant reduction in pain compared to GnRH agonist alone and when used in combination with other hormonal agents (progestin, COC, or GnRH agonist) [61]. Potential disadvantages of AIs include bone loss with prolonged use and development of ovarian follicular cysts. With add-back progestin or COCs, the bone loss does not appear to be significant, and the development of cysts may be less common [62, 63]. There is insufficient data on AIs in adolescents to recommend their use at the present time.

Quality of Life

In the medical management of endometriosis, it is important to consider the quality of life in the adolescent population. Quality of life can be significantly affected by the recurrent pain that is experienced with endometriosis. Compared to unaffected peers, adolescents with endometriosis have significantly worse reports of quality of life [54]. Adolescents with endometriosis have reported mental health diagnoses such as anxiety disorders and depression, difficulties completing daily activities including running or climbing stairs, trouble engaging in social activities with family or friends, inability to attend school, and avoidance of exercise during menstruation more than their peers without endometriosis [54]. An assessment of the patient's quality of life should be included at every visit to ensure treatment is effective and to help the adolescent return to daily social and academic activities.

Final Thoughts

Randomized controlled trials in the adolescent population are urgently needed to evaluate the effectiveness of hormonal suppressive therapies in achieving adequate pain control and prevention of disease progression. Additional studies are also needed to explore long-term options and to evaluate their safety in adolescents. Longitudinal data on adolescents with endometriosis and associated fertility rates is limited, and this offers an opportunity for further investigation. New and emerging research exploring the cellular and molecular mechanisms of endometriosis may help us further understand the disease and create targeted medical therapies. Biomarkers, immunodulators, genetic factors, medicinal herbs, and new medications are under investigation which present an optimistic view of the future treatment of endometriosis.

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Chapter 40
Curcumin in the Management of Endometriosis

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Introduction

Endometriosis is defined by the presence and growth of endometrial stroma and glands outside the uterine cavity. It is an estrogen-dependent chronic inflammatory condition and is associated with pelvic pain and infertility. There are several other endometriosis-associated symptoms such as dysmenorrhea, menorrhagia, dyspareunia, and chronic pelvic pain, but these symptoms are not required for diagnosis. The prevalence of endometriosis is ~10% of all reproductive-age women with a peak between 25 years and 35 years of age [1]. A 0.1% annual incidence of endometriosis among women aged 15–49 years has been reported. The disease is frequent in adolescent women with chronic pelvic pain. In women with subfertility, 21–47% are affected by endometriosis, and in women with chronic pelvic pain, 71–87% have been found with endometriosis [2, 3]. When looking at adolescents suffering from chronic pelvic pain, 25–32.5% have been found to have endometriosis, and approximately 69.6–79.4% of those with chronic pelvic pain who were unresponsive to oral contraceptives (OCPs) or nonsteroidal anti-inflammatory drugs (NSAIDs) also had endometriosis [4–8]. Diagnosis is made only with histopathology confirmation following surgical excision of endometriosis. This disease can be debilitating and extends beyond physical symptoms, with its significant impact on the emotional, mental, and social health of women with this disease. The societal

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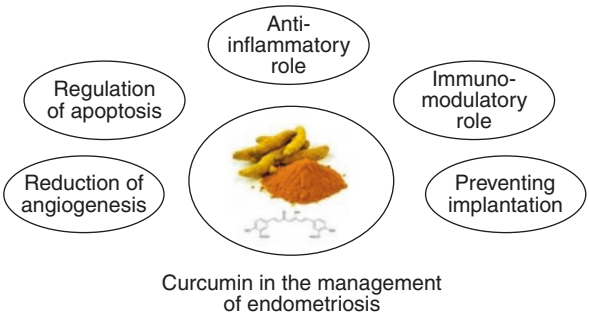

Fig. 40.1 The schematic diagram represents the role of curcumin in the management of endometriosis

burden of endometriosis in the United States is estimated to be approximately 49 billion dollars [9].

Currently, the origin of endometriosis is unknown. The most popular theory surfaced in 1921 by gynecologist John Sampson, who described peritoneal endometriosis by retrograde menstruation through the fallopian tubes [10]. Ninety percent of women have been observed under laparoscopy to undergo retrograde menstruation, but not every woman develops endometriosis, so for many, this theory falls short of explaining all the cases of endometriosis [11]. As a result, other theories have developed such as metaplasia of the pluripotent mesothelial cells lining the peritoneum, mullerianosis which explains endometriosis in the cul-de-sac, and hematogenous or lymphatic dissemination which may explain rare instances of endometriosis in nontraditional locations such as the lungs [12]. These theories may explain physical origins of endometriosis but do not fully explain the pathology involved in its disease state. Eutopic endometrial cells in women with and without endometriosis may appear morphologically and histologically similar; however, there are distinct differences in their behavior [13, 14]. These cells have acquired properties that allow for their resistance to apoptosis and their survival outside the uterine cavity through implantation and invasion of the peritoneum and other sites [15]. Multiple studies have confirmed a genetic alteration in cell adhesion, extracellular matrix remodeling, migration, proliferation, immune system, and inflammation cells of endometriosis which may give insight into its development [16].

This chapter presents the current traditional and both medical and surgical therapies' limitation for endometriosis and the importance of alternative therapy. Moreover, we highlighted the importance of curcumin, a folk medicine in Asian countries, in the management of endometriosis (Fig. 40.1).

Current Treatment of Endometriosis

The etiology and physiology of endometriosis are as elusive as the treatment of the disease. Key in the medical management of the patient with endometriosis is a sound understanding of the patient's pain, fertility plans, as well as the potential side

effects of all therapies. The current options for medical management are limited to oral contraceptives, androgens, aromatase inhibitors, NSAIDs, or oral gonadotropin-releasing hormone (GnRH) agonists. These medications, with the exception of NSAIDs, lead to hypoestrogenic, hyperandrogenic, or hyperestrogenic state in order to suppress endometrial cell proliferation with the hopes of reducing endometriosis [5]. None of these treatments are curative and typically have side effects that make long-term therapy difficult [12]. For instance, GnRH agonists, although effective in the relief of pain symptoms, have adverse effects such as hot flashes, vaginal dryness, mood changes, bone loss, and an impedance to fertility. Even 5 years after treatment, a recurrence rate ranging from 53% to 73% is reported [17].

Surgery via laparotomy or laparoscopy is a common form of therapy used in endometriosis and infertility treatment. It is often performed to remove endometrial implants and adhesions in an effort to restore normal pelvic anatomy. Other goals of surgery can include uterine or ovarian suspension, pre-sacral neurectomy, and transection of the uterosacral ligament, all of which may reduce pelvic pain and future adhesion formation.

Thus, the current traditional and both medical and surgical therapies have failed to provide us with an ideal regimen that would not only bring long-term relief of pain but avoid the adverse effects of current therapy thereby, still allowing for fecundity to occur. This has led to a large effort to find nonhormonal therapy to treat endometriosis, which has resulted in many turning to herbal medicine.

Alternative Therapy

Alternative or herbal medicine is frequently viewed with a level of skepticism and doubt; however, there are many well-known conventional medications with their origins stemming from herbs or plants. In recent years, medicinal herbs and other botanical products have become popular for the management of symptoms of several gynecologic disorders. Evidence for the potential efficacy of medicinal herbs in the treatment of endometriosis-associated symptoms has been reported in the literature [18]. Atropine is derived from belladonna, codeine comes from poppy, salicylic acid is from willow bark, and scopolamine originates from jimson weed [18]. In recent years, medicinal herbs and other botanical products have been gaining recognition for the management of symptoms of several gynecologic disorders [18–20]. Many of these alternative treatments are not novel and have been present since the medical texts of Hippocrates as chronicled by Nezhat et al. [21]. Although none of their texts list gynecologic disorders as we know it today, it can be inferred from their descriptions such as “strangulation of the womb” or “hysteria” that many of the pathologies women struggle with today were also present in the early centuries. Therapeutic remedies included options such as pomegranates, castor oil, tar water, chaste tree, and urine of men and bulls in the form of drinks, suppositories, and fumigants [21]. Pomegranates and chaste tree have been regarded for centuries as contraception and remedies for menstrual dysfunction [22]. Furthermore, it is

demonstrated that pomegranate fractions have preventive and curative effects in obesity, atherosclerosis, hyperlipidemia, inflammation, and bacterial infection [23]. Moreover, pomegranates have anti-proliferative, anti-aromatase, and antitumor properties [24–26]. Perhaps one of the best sources describing early herbal treatments and practices of gynecologic disorders was Greek physician Pedanius Dioscorides' De Materia Medica which composed a highly extensive encyclopedic text of almost 1000 pharmacologic agents [27]. Perhaps even more profound than his text were his forward-thinking views on menstrual pain and recognition of it as a pathologic condition requiring medication [27]. One of his prescriptions for menstrual ailments, horn of hart (red deer), has shown some evidence of possible anti-inflammatory properties to regulate prostaglandins [28].

Perhaps the most promising find in herbal medicine for endometriosis is curcumin, which is derived from turmeric. Signorile et al. [29] attempted to evaluate dietary supplement of a combination of natural ingredients with one of the primary ingredients as turmeric to treat endometriosis. The composition composed the following: "1002 mg linoleic acid (omega 3), 432 mg alpha-linolenic acid (omega 3), 172.8 mg linoleic acid (omega 6), 200 mg quercetin, 20 mg nicotinamide, 400 μg 5-methyltetrahydrofolate calcium salt, 20 mg titrated turmeric, 19.5 mg titrated parthenium" [29]. Ninety women with confirmed endometriosis were divided into three groups and received either all active ingredients, a composition of only linseed oil and 5-methyltetrahydrofolate, or a placebo twice a day for 3 months. Participants were asked to rate their symptoms before and after treatment with a visual analog scale (0 to 10) and have their serum levels of prostaglandin E2 (PGE2), estrogen, and CA-125 evaluated. They found that that there was a significant reduction in pain in the patients treated with all active ingredients compared to those without and a significant reduction in PGE2 and CA-125 levels [29]. The results of this study were paramount in providing support for alternative, nonhormonal therapy in endometriosis, and it also served as evidence for the crucial role curcumin or turmeric has in treating endometriosis in human subjects.

Curcumin

Curcumin, [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]1E, 6E, is a major chemical component of turmeric powder, produced from the rhizome of the plant *Curcuma longa*. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, and 5-methoxycurcumin are collectively known as curcuminoids and are isolated from the spice turmeric, a member of the ginger family. Curcumin, the active bioagent, an element responsible for turmeric's gold color, was extracted approximately two centuries ago by two German scientists, Vogel and Pelletier, from the rhizomes of *Curcuma longa* (turmeric) [30–32]. Pharmacologically, curcumin has been used as a traditional medicinal agent in ayurvedic medicine in India for ~ 6000 years [33]. Curcumin is also used in China, East Africa, West Africa, Asia, and Jamaica. The pharmacokinetic, pharmacodynamic, and clinical pharmacological properties of curcumin have been

extensively studied over the past six decades (>3600 citations in Entrez-PubMed). These studies have demonstrated that curcumin functions as an antioxidant [31–33], anti-inflammatory [31–34], and anti-atherosclerotic [31–34]; inhibits scarring [35], cataract [36], and gallstone formation [37]; promotes wound healing [38] and muscle regeneration [39]; prevents liver injury [40]; and other medicinal benefits [41, 42].

A Potent Anti-inflammatory and Immunomodulatory Role of Curcumin in Endometriosis

There is a rapidly growing body of evidence that suggests a dysregulation of the immune system in addition to inflammation is central to the pathological process of endometriosis. A literature review has revealed that the immune alterations such as increased number and activation of cytokines, macrophages, and autoantibodies, along with decreased T-cell reactivity and natural killer (NK) cell cytotoxicity, have allowed for some women to develop endometriosis [43]. Evidence for this has been reported by Oosterlynck et al., who found the peritoneal fluid in women with endometriosis has increased NK-suppressive activity [44]. It has been well postulated that the immune system dysregulation likely occurs through the abnormal production of chemokines and cytokines that leads to a highly inflammatory state for endometriosis to occur [45]. Accumulating evidence has shown curcumin to have strong anti-inflammatory and antioxidant properties which has led to clinical trials evaluating its potential as a treatment for hormone-dependent and hormone-independent cancers [31–34, 46]. A group of trials evaluated the effects of curcumin on inflammatory markers involved in osteoarthritis and showed that they were able to reduce interleukin (IL)-1β, IL-6, cyclooxygenase-2 (COX-2), erythrocyte sedimentation rate (ESR), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), IL-6, substance P, high-sensitivity C-reactive protein (hs-CRP), calcitonin gene-related peptide (CGRP), and monocyte chemotactic protein-1 (MCP-1).

Our detail studies on curcumin examined its effect on the chemokine and cytokine expression of human endometrial stromal cells from normal women and those affected by endometriosis. Endometrial stromal cells (ESCs) were obtained from age-matched women with and without endometriosis. These cells were then grown and cultured with curcumin at concentrations of 1, 5, 10, 20, and 40 μg/ml for 24, 48, and 72 hours to assess the effect of curcumin on the growth of ESCs of women with endometriosis and those without. In addition, the effect of curcumin on the levels of the following chemokines and cytokine was measured at 24 and 48 hours after receiving curcumin: cytokines TNF-α, vascular permeability factor/vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), interferon γ (IFNγ), fibroblast growth factors (FGF), IL-1β, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, and IL-17 and chemokines eotaxin-1 (CCL11), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF),

IFNγ-induced protein 10 (IP-10/CXCL10), MCP-1/CCL2, macrophage inflammatory proteins 1a (MIP-1α/CCL3), MIP-1β/CCL4, and RANTES (CCL5). At baseline, these studies reveal that eutopic endometrium of endometriosis subjects (EESCs) had higher levels of chemokines and cytokines as compared to normal endometrial stromal cells (NESCs). Also, EESCs had higher levels of inhibitors of NF-κB (IKKα and β), and nuclear factor-kappa β (NF-κβ), c-Jun NH2 kinase (JNK), and signal transducer and activator of transcription 3 (STAT3) which are molecules upregulated in the pro-inflammatory pathway [47]. JNK and STAT3 are involved in the downstream activation of kinases that ultimately converge on NF-κB for the transcription of chemokines and cytokines [46–49]. Following treatment of curcumin at 5 or 10ug/ml at 24 and 48 hours, most of the studied chemokines and cytokines were inhibited with increased doses and time, particularly IL-6, IL-8, IP-10, GM-CSF, MCP-1, and RANTES in EESC. An interesting find in this study was that curcumin increased secretion of IL-10 and IL-12 in a dose- and time-dependent manner, both of which are known to have anti-inflammatory properties that inactivate macrophages and inhibit pro-inflammatory and proangiogenic cytokines and chemokines [13, 47]. Curcumin treatment also significantly inhibited phosphorylation of IKKα, IKKβ, and NF-κB and decreased the expression of JNK and STAT3 [13]. Our study was paramount in its results which not only confirmed that the level of chemokine and cytokine secretion differs between endometrium from women with endometriosis and those without the disease but showed that based on the reported data curcumin treatment could reduce these levels to that of women without the disease.

Other mediators believed to be involved in the pathogenesis of endometriosis are intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) which serve as a chemoattractant to facilitate migration and recruitment of leukocytes from circulation to inflamed site [50]. Both VCAM-1 and ICAM-1 have been found in ectopic endometrial cells [51]. Research has illustrated that human ectopic endometrial cells strongly express ICAM-1 at even higher levels than in the eutopic endometrial cell of patients with endometriosis [51, 52]. Human eutopic endometrial stromal cells have been found to express ICAM-1, but ectopic endometrial cells of a patient with endometriosis have even higher levels of ICAM-1 [51–56]. Expression of ICAM-1, specifically in endometriomas, significantly increases with input from IL-1β and IFN-γ which further illustrates the role of chemokines and cytokines in the inflammatory processes in the pathogenesis of endometriosis [51, 52]. Activation of VCAM-1 in endothelial cells is regulated by input from inflammatory markers, such as TNF-α, IL-1β, IL-4, and IFN-γ, and ICAM-1 in ectopic endometrium [51–56].

Kim et al. sought to evaluate the effects of curcumin on the expression of ICAM-1, VCAM-1, and other pro-inflammatory cytokines: IL-6, IL-8, and MCP-1 in TNF-α-stimulated endometriotic stromal cells of patients with severe endometriosis. The results of the study demonstrated curcumin's ability to decrease TNF-α-stimulated expression of ICAM-1 and VCAM-1 along with other pro-inflammatory mediators through inhibiting the activation of transcription factor NF-kB [57].

Regulation of Apoptosis in Endometriosis Using Curcumin

Endometrial cells from women with endometriosis have acquired a cell survival advantage in the apoptosis process over the endometrial cells in women without endometriosis. Apoptosis is a cellular process in which programmed cell death of unwanted or damaged cells occurs. This occurs regularly through the menstrual cycle. In women with endometriosis, an increased number of proliferating cells, as well as decreased apoptosis, were found as compared to women without endometriosis [58]. The process of apoptosis requires homeostasis in which there must always be a constant state of balance between cell death and cell growth. When there is a defect in the apoptic machinery, pathologic processes may occur such as cancer (infrequent apoptosis) or degenerative (too frequent apoptosis) diseases [59]. There are two pathways involved in this process: intrinsic mitochondrial or extrinsic death receptor pathway. There is a third pathway, the common pathway, in which both pathways ultimately converge on capsase-3 to allow for finalization of apoptosis. The intrinsic mitochondrial pathway involves initiation internally that leads to mitochondrial permeability and release of cytochrome c to activate capsase-9 which will initiate the common pathway. Regulation is controlled by pro-apoptotic proteins such as Bcl-2-associated X protein (Bax) and Bcl-2-associated agonist of cell death (Bad) and anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xl) [59, 60]. The extrinsic pathway, however, utilizes a death receptor Fas (DD95) and its receptor ligand (Fas-L) to eventually activate capsase-8 which also will converge on capsase-3. Meresman and colleagues in a study of endometrial samples of 30 women found that not only did women with endometriosis have decreased apoptotic cells in their endometrium but increased expression of Bcl-2 in proliferative endometrium while Bad expression was absent as compared to controls [61]. This was also confirmed in an earlier study of Mclaren et al., which found peritoneal macrophages of women with endometriosis had higher levels of Bcl-2 expression as compared to controls while Bax-2 was increased in women without endometriosis [62]. Studies have highlighted curcumin's therapeutic potential in targeting apoptosis within endometrial cells. Endometrial stem cells (normal and endometriotic) treated with different doses (1, 5, 10, 30, and 40 ug/ml) of curcumin for 24, 48, and 72 hours resulted in apoptotic cell death in a dose-dependent and time-dependent manner with a 100% cell death at 72 hours for normal endometrial cells; however eutopic endometriotic stromal cells were more resistant to apoptosis [13]. Zhang et al. also demonstrated the apoptotic effects of curcumin. Endometrial stromal and epithelial cells from women with endometriosis and without endometriosis were first assessed and showed that, compared to normal endometrial stromal cells, ectopic endometrial stromal cells had higher growth rate [14]. After an intervention with curcumin of either 10 μmol/L, 30 μmol/L, or 50 μmol/L for 96 hours, the number of endometriotic stromal cells and growth were reduced as compared to the untreated group [14]. A study by Jana et al. reported curcumin's effect of inducing apoptosis in endometrial cells in endometriosis mouse models and the potential mechanism by which it is done [60]. Mice with estradiol

implants treated at different doses intraperitoneally with 12, 24, and 48 mg/kg of curcumin prior to inoculation with endometrial extract and continued for 3 days after showed decrease in number of peritoneal endometrial glands after endometriotic induction. Curcumin treatment also increased Bax expression and mitochondrial permeability suggesting increased permeability for the release of cytochrome C. In fact, cytochrome-c expression was also decreased indicating increased cytochrome-c release into the cytoplasm and consequently apoptosis. This study provided support not only of curcumin's ability to target cell proliferation and apoptosis but presented how curcumin's intervention may be therapeutic [60].

Reduction of Angiogenesis in Endometriosis Using Curcumin

Key to the survival and proliferation of any tissue growth is an adequate blood supply, and the establishment of endometriosis is no exception to this cellular dynamic. Angiogenesis occurs when a growing cell mass is separated by a significant distance of its original vascular supply [63]. Tissue fragment that can serve as a large enough representation of the original tissue architecture requires immediate blood supply due to the metabolic, nutrient, and oxygen demands [64]. One of the most important molecules required in this process is vascular endothelial growth factor or VEGF. It is involved in endothelial cell proliferation, migration, and enhanced permeability necessary for angiogenesis to occur. VEGF is enhanced with estradiol and progesterone, and the concentration changes throughout the menstrual cycle with increases occurring during the secretory phase of menstruation [65]. Shifren et al. found that peritoneal fluid concentration of VEGF increased significantly in women with moderate to severe endometriosis than in women with minimal, mild, or no disease [66]. They also observed that human endometrial cells synthesize and secrete VEGF [66]. Machado et al. established the experimental model of rat peritoneal endometriosis to evaluate the process of angiogenesis and to compare with eutopic endometrium [67]. This study revealed that auto-transplantation of endometrium pieces into the peritoneal cavity mimic endometriosis and lesions were cystic and vascularized, and demonstrated histological hallmarks of human pathology, such as endometrial glands and stroma. The vascular density and the presence of VEGF and Flk-1 and MMP-9 were significantly higher in endometriotic lesions than in eutopic endometrium and confirmed the angiogenic potential of these lesions [66–68]. More importantly there was a significant positive correlation between micro-vessel density, a quantitative measure of angiogenesis, and VEGF protein expression which one can infer that angiogenesis in endometriosis is a VEGF-mediated process [69]. Zhang et al. also presented important findings regarding angiogenesis requirement in endometriosis and the potential role of curcumin in anti-angiogenesis [69]. When curcumin was administered, VEGF expression in ectopic endometrium was decreased in a dose-dependent number as also confirmed by Cao et al. [70].

Preventing the Implantation of Endometriosis Using Curcumin

Initial establishment of endometriotic lesions requires implantation and adherence. This occurs via degradation of the extracellular matrix which constitutes collagen, fibronectin, glycoprotein, and laminin which is accomplished primarily by matrix metalloproteinases (MMPs). This physiologic process occurs regularly in the repair and regeneration of endometrium [71]. Endometriotic implants have shown abnormal or elevated levels of MMPs and their inhibitors [72]. A study by Brunner et al. revealed that suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice [73]. Ectopic lesions were significantly reduced in mice that received TIMP-1 which provided evidence for the role of MMP in the establishment of endometriosis. With increasing severity and duration of endometriosis, MMP-9 activity was upregulated in these mouse models however, application of curcumin pre and post treatment inhibited both MMP-9 activity and expression to control values as well as regression of the disease in a dose-dependent [71]. MMP-2 activity was evaluated by Jana et al. [60] in Balb/c mice induced with peritoneal endometriosis. Following induction, an elevation of MMP-2 activity occurred as well as a decreased expression of TIMP-2; when curcumin was given at a dose of 48 mg/kg body weight once daily for 3 days, MMP-2 activity decreased as TIMP-2 increased. The administration of curcumin was able to delay endometriosis development [60]. Regulation of MMP has gained much attention due to its role in tumor cell invasion and proliferation, and now the therapeutic effects of curcumin in the control of MMPs are currently being evaluated. Sun et al. investigated the effect of curcumin concentrations on the proliferation and invasion of endometrial cancer cells. These authors demonstrated that curcumin can downregulate MMP-2, inhibiting the proliferation and invasion of cancer cells [74].

Pharmacotherapy Challenges of Curcumin

Currently, the major shortcoming of curcumin in its pharmaceutical use is its limited bioavailability. Curcumin has been found to be safe and nontoxic in pharmacological studies [20]. Doses up to 8 g/day are tolerable; however this may be in part to its limited bioavailability as previously mentioned [75]. When administered orally, curcumin has low intestinal absorption and rapid clearance. Guiteres et al. found that the half-life of curcumin is 8.64 ± 2.31 (IV) and 32.70 ± 12.92 (oral) minutes [76]. Yang and colleagues investigated curcumin's bioavailability in a rat model [77]. Following 10 mg/kg IV and 500 mg/kg oral administration of curcumin in mice, bioavailability was approximately 1% [77]. Also, studies indicate that following the metabolism of curcumin its metabolites may differ from its parent and the potential benefits may be lost or reduced [20]. Multiple strategies have been

employed to overcome the challenges of curcumin bioavailability such as the combination of nanoparticles, liposomes, adjuvants, micelles, and phospholipid complexes. Nanoparticles increase aqueous distribution of a hydrophobic drug, liposomes act as a delivery system of hydrophobic and hydrophilic drugs, adjuvants inhibit pathways responsible for rapid clearance, and micelles or phospholipid complexes enhance gastrointestinal absorption [75, 78]. Perhaps the most promising strategy may be one that avoids the oral route for the administration of curcumin and instead uses an intravaginal delivery system such as a vaginal ring. Sahoo and colleagues detailed the use of the vagina as a drug delivery system. With the vagina's rich vascular supply, it has the advantage to bypass the first-pass metabolism of the gut and hepatic system thereby providing greater bioavailability and possibly offering more efficient and faster supply to reproductive organs. Vaginal rings are mainly used for contraception and provide sustained and controlled release of drugs usually through a circular ploy or silicon device ring. Drugs at the surface of the ring release drugs faster than the inner layer. This system could provide increased efficacy and compliance, thereby eliminating interruption in therapy and achieving long-term treatment with curcumin [79].

Future Studies

Multiple bodies of evidence have shown that endometriosis is an estrogen-dependent disease with higher levels and abnormal estrogen receptors seen in women with endometriosis [14]. Many of the studies cited here utilized estrogen stimulation to achieve endometriosis in animal models. Endometriotic lesions have estrogen and progesterone receptors in addition to aromatase; however, these receptors and the metabolism of estrogen in endometriosis have been shown to differ from those in women without endometriosis [79]. We continue to learn more of the role of curcumin in the targets for molecular mechanisms involved in the inhibition or reduction of endometriosis. However, we have limited information with regard to its role in hormonal regulation. The study by Zhang et al. [14] is one of the only studies to provide evidence that curcumin inhibits endometriosis in endometrial cells by reducing estradiol production. They showed that at baseline there was increased estradiol production by in vitro endometriotic cells; however, after treatment with curcumin, cell growth and estrogen levels were reduced. Curcumin's anti-inflammatory, anti-proliferative, and pro-apoptotic effects may offer a well-tolerated alternative to standard approved anti-endometriosis medications. Nonhormonal therapeutics of plant origin may be especially suitable for young women with severe symptoms of endometriosis-associated pain who require a protracted duration of therapy. Additional experiments are underway to elucidate curcumin's precise anti-inflammatory and potential fertility-preserving effects in in vivo models of endometriosis. We have provided evidence that support future use and investigation of curcumin as a natural and safe alternative therapy or as an adjunct for those with limited improvement in current medical therapy for endometriosis treatment.

Conclusion

In this chapter, we have only highlighted a few of the studies in the numerous bodies of work that provide evidence for the role of curcumin in the fight against endometriosis. The therapeutic potential of curcumin may serve as an alternative or adjunct to many current hormonal treatments available. Endometriosis is likely an inflammatory-driven process with similarities to many autoimmune processes. Curcumin has been shown to have anti-inflammatory properties through inhibition of multiple pro-inflammatory mediators. Curcumin also has the ability to inhibit the cell attachment, proliferation, and survival of endometriosis through its anti-angiogenic and apoptotic properties. We are still limited in our knowledge of its effects on estrogen and the appropriate mode in which to administer it for its full effect; however, with more directed studies and trials, a medically formulated curcumin could make its way on the market and lessen the current burden of endometriosis in the world.

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Chapter 41
The Holistic Approach to Managing Adolescent Endometriosis

Christina Davis-Kankanamge

Introduction

A holistic approach is taking the whole body into account including physical, mental, emotional, and social in order to treat an ailment, such as endometriosis. This could also be considered a treatment of mind and body. This chapter aims to describe holistic therapy for the adolescent woman with endometriosis. The medical treatment of endometriosis is covered elsewhere, and this chapter focuses on nonmedical treatment including pain management alternatives in the treatment of adolescent endometriosis. Discussion between mental health and physical health, nutrition, exercise, stress reduction techniques, sleep, and pain management via complementary and alternative medicine is also included. The holistic approach is not meant to be used in place of medical and surgical therapy; however, it is to be used as an adjunct to medical pharmacologic therapy such as estrogen and progesterone pills, nonsteroidal anti-inflammatory drug, and gonadotropin-releasing hormone agonists. The holistic approach focuses on improving the quality of life which allows improved function via multiple different aspects of the patient's daily life. A careful assessment of the risks and benefits should be undertaken prior to recommendation. Most modalities discussed here have few adverse effects which can be attractive to patients.

There is limited peer-reviewed literature in the treatment of endometriosis in the adolescent regarding holistic therapy. There has been literature supporting holistic care in adult endometriosis since at least the mid-1990s [1]. A systematic review published in 2018 identified eight studies which evaluated complementary treatments for women with endometriosis [2]. Of those therapies reviewed, acupuncture was the therapy with clinically significant improvement. The other therapies had a positive trend but were

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not statistically significant. This chapter covers adolescent literature where available and otherwise includes adult female data if no adolescent data was found.

Brief Ancient History of Medicine for Treatment of Female Pain Disorders "Strangulation of the Womb"

Historically, there are descriptions of symptoms of menstrual pain in art, literature, and scientific texts dating to the fourth and fifth centuries BC in the Hippocratic texts. (1) Most of the therapies were ingestible, inhaled, or placed via suppository. One substance is the pomegranate which has been investigated for its antiproliferative and antiaromatase properties related to breast cancer cells. (2) Another substance used was both bull and men's urine. Biochemical studies published in 1938 show some antiestrogenic effects of bull urine (3).

Dioscorides who authored *De Materia Medica* (~77AD) included pharmacologic compounds including "Horne of an Hart." This is possibly in reference to a red deer species found in Europe and Asia Minor. (1) It is interesting that red deer antler is used in traditional Chinese medicine and that in animal studies, antler velvet products may "produce anti-inflammatory compounds that assist in the regulation of prostaglandins" (4).

Even as these remedies are "ancient", they have been passed forward and can be found in therapies used in today's society [3–6].

Nutrition

A key part of whole body medical therapy is the inclusion of nutrition and diet. This can be via daily food intake or supplementation via herbal preparation. This section covers possible diets that can relieve endometriosis pain as well as Chinese herbal medicine.

There are current theories that endometriosis has an underlying excessive inflammation aspect or autoimmune component. A fairly recent development has been the adoption of certain diets. Some recommend a low inflammatory diet similar to diets used for irritable bowel syndrome. Both irritable bowel syndrome and endometriosis share visceral hypersensitivity [7–9].

The thought is by decreasing certain inflammatory foods, inflammation is not only the gut but also the endometrial tissue. Use of the FODMAP diet was adopted for treatment of irritable bowel first and has since shown some effectiveness in the relief of gastrointestinal symptoms [10].

FODMAP is the acronym for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, a group of short-chain carbohydrates found in a variety of fruits, vegetables, and grains [11]. The foods are thought to lead to an increase of bacteria within the gut which leads to increased intestinal permeability and

epithelial irritation of the colon. FODMAP foods include fruits, honey, wheat, onions, milk, yogurt, apples, pears, reduced caloric sweetener, legumes, cabbage, and brussels sprouts [12].

Vitamins are a different avenue of research for treating symptoms of endometriosis. There have been mixed results. Vitamin supplementation does not help with endometriosis-related fatigue [13]. Some findings from a different study suggest that greater predicted plasma vitamin D levels and a higher intake of dairy foods are associated with a decreased risk of endometriosis [14].

Traditional Chinese herbal medicine has been used routinely for many years to treat endometriosis pain as well as a variety of ailments. Tradition medicines include herbal teas, pills, intramuscular injections, and enemas. There is significant research; however, there are limited high-quality randomized controlled trials [15]. The herbal supplements described in the study were NeiYiWan pills taken orally and an herbal Nei Yi enema. The pills are made from a variety of herbs [Dan Shen (Salviae miltiorrhizae Radix), Xue Jie (Draconis Sanguis), San Leng (Sparganii Rhizoma), E Zhu (Curcumae Rhizoma), Tao Ren (Persicae Semen), San Qi (Notoginseng Radix), Dang Gui (Angelica sinensis), Gui Zhi (Cinnamomi Ramulus), Xiang Fu (Cyperi Rhizoma), Niu Xi (Achyranthis bidentate Radix)]. The two small studies suggest that Chinese herbal medicine may be as effective as gestrinone and danazol in relieving endometriosis-related pain with fewer side effects; however, the studies were small and of limited quality [15].

Musculoskeletal Modalities

There are many forms of physical adjunctive therapies whether they are performed by the patient or a practitioner. These can include exercise, chiropractic care, acupuncture/acupressure, and massage/soft tissue manipulation.

Exercise can be significantly helpful in the reduction of anxiety and depression which are often present in adolescents and women with endometriosis. Endometriosis can also decrease the amount the person exercises daily as there is progression. This can and would decrease a person's quality of life which can in turn lead to increased rates of depression.

Types of exercise such as yoga can be beneficial. This is likely due to the meditative aspects as well as core stretching included in yoga. Yoga allows the practitioner meditation practice by slow breathing and body awareness. Stretching abdominal core muscles can assist in lessening chronic musculoskeletal pain and pelvic floor dysfunction. Musculoskeletal pain can contribute to endometriosis pain as an additive effect on the pain the patient might solely associate with endometriosis. By improvement of part of the abdominal pain, there can be improvement in the quality of life, which allows the patient better functioning.

Chiropractic care is the manipulation of the spine to correct subluxations or misaligned bones. By manipulating the misaligned bone joints, this can improve nerve, muscle, and lymph function. Chiropractic care is often performed over a series of

visits with manipulations at each visit. A chiropractor will base their treatment plan off of the complaints and the amount of manipulations needed to correct the problem. High-quality evidence supporting chiropractic care is lacking; however, the risk of adverse effects is small with a skilled and trained provider.

Acupuncture is the treatment "qi" by treating blockages along meridians via a nerve stimulation with solid needle placement in the skin. Acupressure is the treatment of the meridians via nerve stimulation by gentle pressure. There is evidence of efficacy in acupressure/acupuncture for treatment of endometriosis [16, 17]. Acupressure is generally more accepted in pediatric and adolescent patients than acupuncture. Acupuncture is generally safe when performed by trained professionals [18].

Massage, also known as soft tissue manipulation, can be beneficial in reducing musculoskeletal pain by assisting the muscles in relaxation. This can be done by trigger points or areas of muscle tightness which are released via pressure. Transcutaneous electrical nerve stimulation can also be used on the skin to assist in relaxation of the muscles. Rigorous clinical trials need to be performed to evaluate effectiveness.

There are different levels of training and certification for practitioners of these modalities. Please consult with your local specialist in their respective area to confirm expertise and experience.

Stress Reduction

Stress reduction can benefit endometriosis patients through a variety of mechanisms. One mechanism is decreasing the inflammatory response in the body. Another mechanism is that by reducing stress, sleeping improves. A well-rested person is able to function better.

Sleep is vitally important whether one has endometriosis or not. Teenagers, 13–18 years of age, should sleep 8–10 hours per 24 hours on a regular basis to promote optimal health [19]. This allows the body to heal and recuperate from the day's activities. Adequate sleep can also decrease additional pain symptoms such as migraine headaches and improve mental disorders such as anxiety and depression that are often associated with endometriosis. Fatigue is an underestimated syndrome of endometriosis as it affects the majority of women with endometriosis; however, it is not widely discussed in the literature [13].

Counseling with cognitive behavioral therapy assists the patient in verbalizing the pain and functioning through the pain. Improvement of coping skills can also result from cognitive behavioral therapy. As depression and anxiety can be present in conjunction with endometriosis, counseling can assist with a decrease in symptoms and an improvement in patient functioning. Journaling and mindfulness of pain used in addition to counseling in pain management can be very beneficial in improvement of activities of daily living. This aspect of treatment of endometriosis

in the adolescent has not been studied; however, these likely benefits can be extrapolated from adult endometriosis and chronic pain literature.

Multiple children's hospitals in the United States have multidisciplinary pain centers. These centers include a variety of specialties (Pediatric Gynecology, Gastroenterology, Psychology, Physical Therapy) and offer both pharmacologic and non-pharmacologic treatment modalities. An individualized, multidisciplinary approach may be effective in improving overall outcome in patients with chronic pelvic pain by reducing pain and normalizing function [20]. It is important to weigh risks and benefits of all interventions as adolescents have most of their reproductive lives ahead of them and so interventions should be optimized to minimize progression of disease. The overall goals of treatment should include optimizing function, minimizing pain and adverse effects, as well as setting appropriate expectations.

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Chapter 42
Endometriosis: The Teacher

Theresa Wright and Ceana H. Nezhat

The writing of this is serendipitously timed. Had I written of endometriosis 30 years ago, the content would have been dense with sadness and pain. Even 10 years ago my journey would have read much more helpless and hopeless than today. From my current vantage point, I can see the invaluable lessons and benefits inherent in this ailment. I can touch the innate wisdom this complex has provided and that is priceless!

What I share here is unique as it is a personal account; however, the principles inherent within are universal. It is important to clarify from the outset that dysfunction transcends all facets and functions of life, as does endometriosis. Dysfunction does not discriminate. It impacts each human, at some point, on some level, regardless of economic, social, gender, age, or any other status. There is no such thing as a perfect parent, a perfect childhood, a perfect job, a perfect marriage… these are fantasies the mind conjures in order to avoid dealing with reality. Denying the presence of dysfunction in our lives is primary, unsophisticated, fear-based egotism. It is blatant negation of our humanness. This repression is at the root of our feeling not smart enough, not good enough, not lovable, worthless, tainted… the list for each of us is different but all lead to the same end. Continued suppression of these energies causes them to crystalize into dense matter, manifesting as disease in the body. Here, we concern ourselves with endometriosis.

Seen from a higher perspective, it becomes obvious that dysfunction is curiously life affirming. It stretches us. It is potentially a powerful catalyst for those willing to change. It is a signal that something is not working. If we are willing to listen, dysfunction points the way to higher growth. Whereas the word dysfunction is often used to direct and assign blame, shame, and guilt, as in "Who or what caused the dysfunction?", I am convinced that it is actually part of an intelligent, organized

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structure, compassionately pointing us to imbalances in any given system. Whether we speak of core family dysfunction or social, cultural, collective, or even our individual physical dysfunction, it is a potent indicator for us to recalibrate and return to homeostasis.

There is no judgment of anyone or anything intended in what I share. Judgment impedes the very understandings we seek. My singular interest is in sharing my journey and my own insights and discoveries, over many years of exploration, with my fellow beings whose lives are impacted by this disorder.

Be it clear that at the heart of all I convey is a great respect and compassion for the full spectrum of the human condition and an honoring of life itself and the lessons it imparts.

Growing Up and Living Undiagnosed

The seventh of eight children, I was the "good girl." Born into the midst of a dysfunctional home environment, I learned to stay out of the way, not daring to tempt trouble or be a source of burden to anyone. Grateful for having only the most basic needs met, invisibility became an art form. I decided early on there were others with more pressing needs than mine, assuming the role of emotional and eventually physical caregiver. Today, this is commonly known as co-dependency. As a young one, being adept at reading other's moods, as well as the emotional temperature of an environment, was not only a gift but a necessity. Distancing and sometimes completely separating from my own body as a form of protection from chronic trauma was simple self-preservation.

I attended strict parochial schools. In this setting, the role of "good girl" further escalated to perfectionist as I excelled academically, athletically, and socially. It became evident that these success-oriented behaviors earned approval not only on the home front but with elders, teachers, peers, and society at large. Pleasing others and keeping the peace, even to the detriment of my personal well-being, were preferred to the base fear of rejection, abandonment, and jeopardized safety.

Observing how people responded so positively to my amiable demeanor, I believed I had life figured out! I could finally relax the tightly held fist of anxiety I had engaged so long. Learning to play the game of giving others what I deemed they wanted gained me acceptance and love. I based my very value as a human being on this external barometer. Unknowingly, I had become enslaved unto my own custom-styled existence of self-repudiation.

The start of my menstrual cycle came at 16 and with it, unfathomable pain, migraine headaches, mood imbalances, and a plethora of other manifestations. My mother, 58 at the time and pregnant most of her adult life, did not exhibit any external signs of endometriosis. This was not unusual since pregnancy is one of the suggested protocols to keep this condition in remission. I have no doubt, however, that

her myriad of other health issues were a result of the body's attempt to cleanse itself. She may not have had endometriosis per se, yet her physicality reflected an unhealthy system in a host of ways. Dis-ease is still disease although the symptomatology presents differently.

Mother could not relate to my ailments. We never once discussed the body, menses, sexuality, and certainly not feminine desires. Unskilled and uncomfortable in communicating about what was deemed unsavory subject matter, she assumed and insinuated I must be doing something "bad," code for "having sex," to have brought this curse of painful periods upon myself.

Moreover, a visit to the doctor for a simple case of menses was an unjustified expense. Her line of thinking was "this is a natural process, an indoctrination into womanhood." It was something I would have to accept. Women suffer – that's just the way it is. Suffice to say, I felt very alone.

Most assuredly, mother was a kind and deeply loving woman. This way of addressing my pain was born of her own misunderstandings and lack of parental support. She came from a generation and background where such matters were never considered for discussion. It was evident that she was tormented by her helplessness to ease my pain and so came the projection of her own guilt and shame onto me. Undoubtedly, there was no ill intention on her part, and the logic is seen as so very innocent now. That something may be awry with my health was not thought to be a possibility. And so, in the absence of astute professional care, endometriosis was never part of the equation.

Throughout my teens and twenties, the pain associated with my moon cycle became more severe. What was initially a once monthly pain now became all-month-long agony. Studying to be a dental hygienist, I had the opportunity to learn about the body in depth. Anatomy, physiology, nutrition, and pharmacology were my favorite subjects. I poured myself into school, engaged in an active social life, and regularly attended to the needs of my aging parents. I was also working to pay for school so there wasn't much time to pencil in for sleep. Chronic stress. Adrenal duress. I didn't perceive it as problematic though it felt so familiar. The silent philosophy engrained from the earliest years was "a life without stress is an entitled, selfish life."

Migraines, heavy clotting, lower back pain, abdominal distention, painful intercourse, generalized inflammation, severe allergies, anxiety, painful urination and defecation, chronic sinus and chest infections, fibromyalgia… it was no wonder that during a routine visit, my gynecologist discovered a lesion on my thyroid. Something had to give, and yet, there was still no mention of endometriosis.

Newly engaged at the time, a hectic social life, taking on the role of stepmom to two active, toddler boys – there was no time to be ill. "Ill" isn't fun. "Ill" isn't sexy. "Ill" is an inconvenience to others. In addition, I was managing a rapidly expanding dental practice while working a full schedule of patients. Sleep and downtime were luxuries, not necessities. Following a partial thyroidectomy I began daily thyroid supplementation which continues today.

After thyroid surgery I immediately did what I needed to do, jumped directly into my previous routine without ever questioning the possibility that there was a valuable message for me in all these symptoms. Dietary changes, exercise, a more relaxed lifestyle – these were never suggested and to add them to an already weighty schedule would have only created more stress. This is what I told myself anyway. And besides, taking time to care for my own needs when others were depending on me would have been, yes, selfish!

What I know now is that a change in lifestyle was the very medicine I needed for healing. Nurturing, sweetness, tenderness, succulence. The feminine thrives on lushness and shrivels in the dryness of life. Had someone only explained this to me… which is why I am moved to share with you.

After marrying I considered myself incredibly fortunate to become pregnant. I wanted to be a mother more than I wanted any other thing. Not surprisingly, I experienced challenges during the pregnancy and our daughter arrived with her own medical issues. Due to complications with her birth, I was told I would never be able to conceive again. Miraculously, shortly after our daughter stopped nursing I became pregnant with our son. He nursed also. In terms of endometriosis this meant three full years without a cycle, and for me, substantial relief from excruciating menstrual pain.

The Long-Awaited Diagnosis and Treatment

Once our son stopped nursing, the symptoms immediately returned, now with a vengeance. So did the resumption of a hectic lifestyle. The following year I returned to the gynecologist with unbearable pain. It was at this point that the diagnosis of endometriosis was made – a long time in the making. Now, well into adulthood, the opening had come to begin unraveling the twisted threads that led up to this moment. The nemesis finally had a name. Odd as it sounds, I felt great relief knowing there was a label to site when attempting to explain my pain. This was officially no longer "all in my head." I was certifiably sane.

The diagnosis of endometriosis was truly the beginning of a great opportunity for healing.

At the time of my diagnosis, endometriosis was quite the perplexing disease. Few doctors had extensive experience in treating this condition, and the research on causative factors was limited. Following an exploratory procedure, my doctor recommended immediate treatment since several organs were already involved. It was an extraordinary blessing that within days I learned of the Drs. Nezhat and their remarkable success with non-invasive procedures for endometriosis. In August 1988 I flew to Atlanta for a consultation and laparoscopy. I have been receiving exemplary treatment and service from the doctors and staff at Nezhat Medical Center and Northside Hospital ever since.

Multiple surgeries involving various organs, birth control, hormone replacement therapy, and eventually a hysterectomy followed. All of this while doing what I loved most – caring for family. By this time I had taken on full responsibility for the health care and personal affairs of my parents as they had both undergone total laryngectomies. It is still difficult to sit with the impact endometriosis has had on this life. Moreover, it is impossible to attempt to explain the devastating effects of this disease to those who have not experienced it firsthand.

Coping and Support

Those who love and care for us need to know, however, that women with endometriosis aren't broken. They don't need fixing. And for that matter, no doctor can permanently cure endometriosis; they can only serve to support the process by which, through steadfast commitment of the host, the body heals itself. I am convinced that ultimately the healing of endometriosis is an internal job, supported and nurtured by external means.

So what does the woman with endometriosis need? We need to be heard when we cannot hear, nor understand ourselves. We need assistance during times of confusion when we cannot make clear decisions. We need the patience and tenderness of those who will bear witness to our pain without pushing or wishing it away. We need to be reassured of our value, not for our appearance, or for what we are doing, but for our very being. We need to be reminded to breathe, and that someone has our back, and that everything is being taken care of so we can focus on caring for ourselves during the challenging episodes. We need to be met with acceptance, especially when we are rejecting ourselves.

There is deep grief that rises up when endometriosis is active and it is crucial that we be allowed to express this grief widely and openly, without the suggestion that we are "crazy." Even the smallest gesture that reinstates calm, elevates the spirit, and restores balance is of great benefit. An atmosphere of quiet, softness, kindness, and encouragement goes a long way to sustaining a woman on her journey of understanding, and eventually thriving, while managing this complex. This is how we return women to themselves. This is how we return them to their natural, supple, flowing feminine qualities that so endear us to them in the first place. Women with endometriosis did not cause this disease. They did not consciously choose this. Although it may feel like it at times, this is not a punishment. The silence and stigma around endometriosis must be brought into the light of our collective awareness so women may embody their fullness, reclaiming the wholeness that they are.

Daughter Diagnosed

In the depths of my explorations, an even deeper purpose was born for me. About the age of 11, as my beautiful young daughter was approaching adolescence, the signature signs associated with endometriosis began appearing. Due to a strong genetic history, we came to Atlanta, GA, to see Dr. Ceana Nezhat. He made the diagnosis and began treatment immediately.

As parents we may reflect on our childhood and vow not to repeat the errors of our upbringing. What we fail to understand is the "history" we vow not to repeat is imprinted upon us, existing on a deeper level than the physical. It is this root we must excise if we are to forge permanent change.

From birth, my daughter had an inexplicably profound bond with my mother. As mother lived with us, their exceptional connection continued to grow. Without knowing, we were reconciling the "mother wound." There we were, three generations, touching the mystery in tethered communion, healing each other. Although mother has passed, this lofty aspiration continues today.

In the final analysis, what can I offer my daughter as she faces the challenges of endometriosis? When I, as her mother, question my own outdated patterns of thinking and modes of behavior, reconciling the hostilities within myself, my daughter's own conditioning rectifies. This return to peace within ourselves can span generations.

My daughter and I, individually and in partnership, put healing and thriving at the helm of our lives. A spirited interest in endometriosis and exchanging practical means for reclaiming vibrant health are two of our common interests. We are devoted advocates for the realignment of women unto their most independent, robust, and stellar selves.

Adolescent anxiety, bullying, sexual abuse and trafficking, body dysmorphia, obesity, depression, murder, rape, and suicide have all hit unprecedented numbers. Disorders previously demonstrated almost exclusively in the adult population are infiltrating our youth in growing numbers. Rushing children into adulthood has not only psychological and emotional implications, but it is aging the physical body as well. I stand resolute in my conviction that endometriosis is just one of many disorders and diseases that are coming to the surface as we prepare for unparalleled strides in healing. Viewed as such, what on the surface appears catastrophic may actually be a significant doorway to our individual and collective evolution.

We want an answer. A single answer. It is the nature of the human to desire complete restoration in one fell swoop. But we are ever evolving beings. Millions of cells die off as new ones turn over each day. Our organs from last year, last month, last week, this morning… they are not the same but in a constant state of transformation. Expressions of endometriosis in the body are responding endlessly to even the most subtle shifts in our thoughts, emotions, and behaviors. It is believed by some to be an "immune dysfunction disorder." I believe it would be more aptly

termed "immune brilliance." It is the organic, divine intelligence of the being, from the grossest to the most subtle parts, that is bidding us to drop the sense of victimhood and tap into our own abilities, thereby activating the healing process.

Not for a moment am I suggesting that we don't need a doctor who specializes in the treatment of this complex disorder. Endometriosis can be seriously aggressive. A skilled specialist is indispensable and an absolute must. On the contrary, becoming a schooled investigator, a true explorer of one's own body/mind/spirit, by definition means engaging others with varied expertise to work in tandem. Self-healing does not mean healing yourself, by yourself. Rather, I'm suggesting a return to self-empowerment by procuring a team of professionals and laypersons who are committed to our highest good. I advocate enlisting those who are aligned with one's personal philosophies.

It is imperative that we seek out honest practitioners, those not focused on notoriety or looking to play the role of magician or God. Instead, doctors whose purpose is to serve. Those interested in working in partnership with the patient as well as with other professionals to discover fresh, innovative, creative ways to unlock the mysterious tapestry of this inflammatory disease. These altruistic health professionals, aware or not, are participating in the healing of not only the individual patient but the entirety of the female collective. When we engage to address the core of endometriosis, we are healing generations both past and future. And as quantum physics demonstrates, we are healing all of these concomitantly in this here… in this now.

Diet and Exercise

We each intuitively know what works for our specific body type. That said, it is what I do proactively on a routine, consistent basis that allows me to partner with my specialist and directly participate in my own healing. We are each responsible to ourselves to keep continually abreast of the latest research and we each have our own preference. I am not a doctor, nor do I hold any certification as a nutritionist. I am, however, well studied in what works for my own body and that is what I am sharing here.

I have found a clean diet of fresh, whole, locally sourced, plant-based, organic fruits and vegetables is best for me. For those who choose, organic dairy, free-range eggs, fish, and grass-fed meats can also be good sources of fats and protein when consumed sparingly. Eliminating gluten, corn and corn products, sugar, white flour, and processed foods in general keeps the body feeling light and clean. This is particularly important on the days leading up to menstruation and during flare-ups.

I reiterate, my findings are a result of direct discovery and what works for one may not be as effective or even recommended for another. Be cautious before taking

supplements as they may interfere with your medications and/or treatments. The following is what I have found beneficial.

Movement	Whatever you choose, just move! Dance, team sports, tai chi, golf, swimming, yoga, rock climbing. Consistency is key. Whichever form of exercise we choose, it must be accompanied by gentle stretching to open the constricted spaces to allow oxygenated blood and charged energy to flow through unimpeded, thereby cleansing and nourishing all organs.
Cleansing	This is not about a fad fast. What I'm referring to is cleansing the physical system slowly and gently, on a daily basis. This can be as simple as choosing lighter foods, juicing for one meal, drinking fresh, clean water, or incorporating lemon, ginger, and other medicinal herbs into our diets. More rigorous fasting can be quite useful in some cases.
Conscious breathing	There is not enough to be said about conscious breathing. Stop! Just stop for a moment. Inhale one long, slow, deep mindful breath and infuse the body with invigorating prana. Depending on our state in the moment, the breath can bring us up from a mundane, tamasic, robotic state on the one end or down from a rajasic, stress-ridden state on the other. Either way, the breath brings us back to our center, reminding us on a deep level that we are alive. The breath connects us to others and to the life confirming natural world that surrounds us.
Meditation	This may mean sitting in silence with your legs crossed. It may mean journaling, cooking, walking, humming, or bathing a baby, an animal, or yourself. You know what allows you to relax. Whatever it is, even for just a few minutes, create the space to do it!
Feeding the senses	Your favorite movies and music. Aromatherapy. Art, literature, poetry. Insightful conversation. Running your hands through a stream of cool water. Deep communing. These are truly food for the soul. The sights and sounds of our environment impact us long after they have faded into the background. We are a sum total of what we imbibe. Choose wisely. Make it great!
Water	Water cannot be overrated. Water flushes and hydrates the cells so vitamins, minerals, and nutrients can be transported throughout the organism. Each and every function of the body relies on water to promote and sustain a healthy internal environment. Tired? Drink water. Hungry? Choose water. Depressed, anxious, angry? Again, water. Thirsty? Go directly for the water.
Spirulina	Early on, long before the re-popularization of using food as sources for healing, my specialist suggested incorporating *spirulina* into my daily diet. As my body is sensitive, I noticed immediate results. This blue-green algae is a powerful antioxidant and immune system booster. It blends easily into a morning smoothie and I have noticeably more energy and mental clarity. Numerous studies have shown *spirulina* supports the digestive system and has antimicrobial properties, both of which are important, as optimal gut health is critical with any disease.
Turmeric	I have found turmeric to be excellent for reducing inflammation in my joints, abdomen, and even pressure during migraines. In addition to daily supplementation, I also enjoy using it in savory dishes.
Ashwagandha	Ashwagandha is an adaptogen said to assist the body in managing stress. Personally, it has proven beneficial in reducing symptoms of anxiety and depression while moving through the demands of an increasingly fast-paced world. I have also noticed an increase in mental clarity and ability to focus while using this medicinal herb.

Learning is continual and ever expanding; the essence of this message will endure. Endometriosis, as all disease, is a function of imbalance, misalignment, and disharmony, encompassing the mind/body/spirit organism. It is our charge to return ourselves to wholeness. I applaud the fine health professionals who work tirelessly to bring us into a new era of partnered healing. I rally behind those who bravely walk this journey and are willing to step up and share their stories. Accolades to those who love and bolster us – we are forever appreciative!

Endometriosis is my lifelong teacher. It may also be yours.

"Trust your wound to a Teacher's surgery.
Flies collect on a wound.
They cover it, those flies of your self-protecting feelings, your love for what you think is yours.
Let a Teacher wave away the flies and put a plaster on the wound.
Don't turn your head.
Keep looking at the bandaged place.
That's where the Light enters you.
And don't believe for a moment that you're healing yourself."
– *Rumi*

Part XII
Post-operative Considerations

Chapter 43
Complications of Endoscopic Surgery for Adolescent Endometriosis: Prevention, Recognition, and Management

Gustavo Stringel

The management of adolescent endometriosis requires a team approach. It is important to plan and have the resources and help available, especially when there is a complication or an incidental or unexpected finding. Endometriosis has been defined as the presence of endometrial glands and functional stroma outside the uterine lining [1, 2]. The incidence of endometriosis in adolescents has been reported to vary from 19% to 73%. A review article reported 880 adolescent patients with dysmenorrhea or chronic pelvic pain, where the prevalence in patients with chronic pelvic pain was 75% and in patients with dysmenorrhea 70% [1–11].

Laparoscopy for chronic pelvic pain is more often done by gynecologists. However, other specialists also do diagnostic laparoscopy in adolescent patients, including general surgeons, urologists, and, more commonly, pediatric surgeons. The experienced gynecologist readily recognizes the presence of endometriosis even at early stages. However, it may be difficult for a surgeon of another specialty to recognize the problem and to realize that the definite diagnosis of endometriosis needs to be confirmed by biopsy of the lesion and histological confirmation [1–11] (Figs. 43.1, 43.2, 43.3, and 43.4).

The adolescent gynecologist may need to have experts available to assist, in particular in cases when there is a complication or incidental finding, as well as for a reassuring second opinion [12]. It is often the author's decision to scrub with his adolescent gynecology colleagues to assist with laparoscopic endometriosis excision, help with complications, do difficult appendectomies and lysis of adhesions, or deal with other incidental findings. He has found this collaboration mutually educational and gratifying and also beneficial to the patient. Pediatric surgeons operate in small patients weighing only a few pounds to obese adolescents. They also perform operations on multiple systems. The non-gynecological surgeon operating in patients with chronic or recurrent abdominal pain needs to be able to recognize

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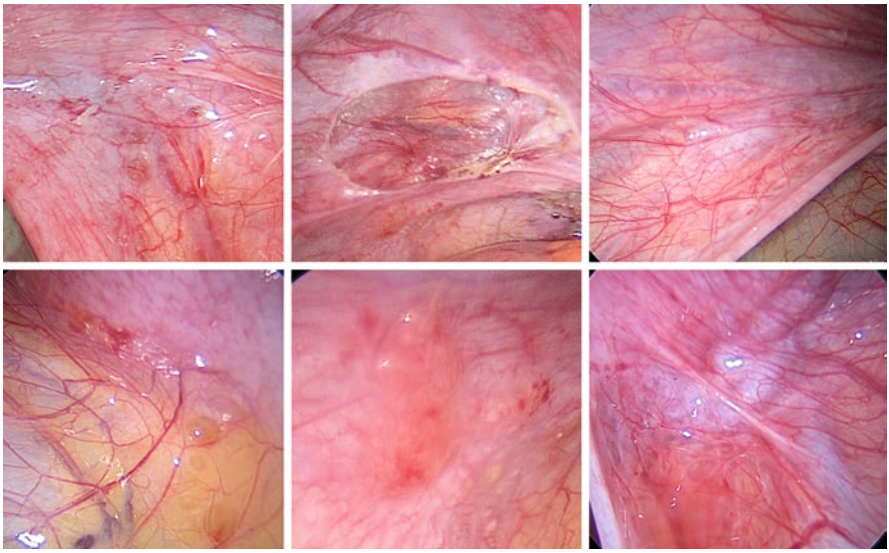

Fig. 43.1 Endometriosis of the peritoneum found during diagnostic laparoscopy. The diagnosis had histological confirmation

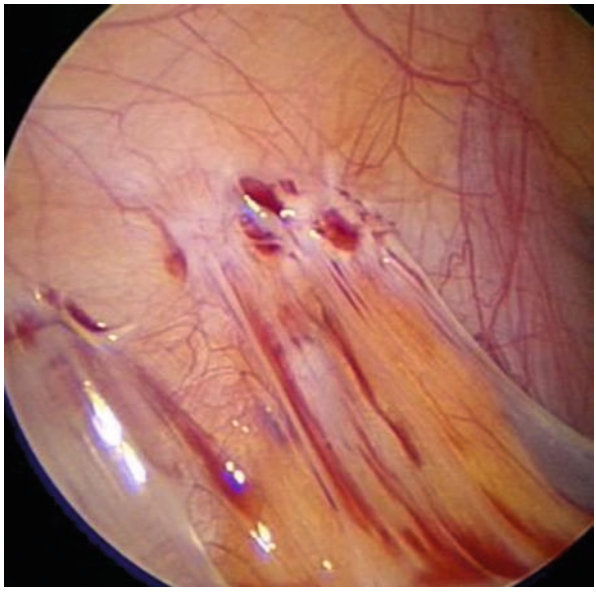

Fig. 43.2 Endometriosis of the abdominal wall

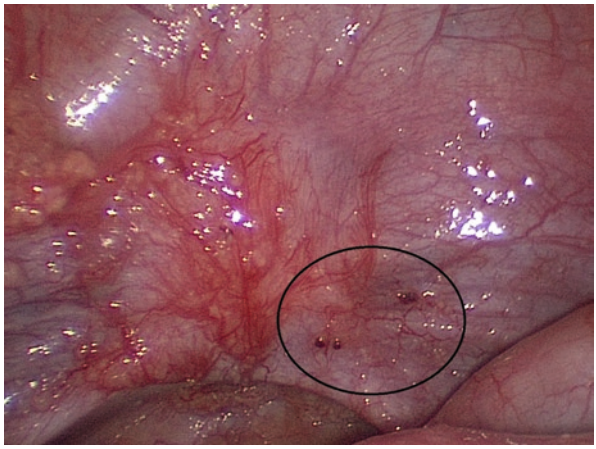

Fig. 43.3 Endometriosis nodules

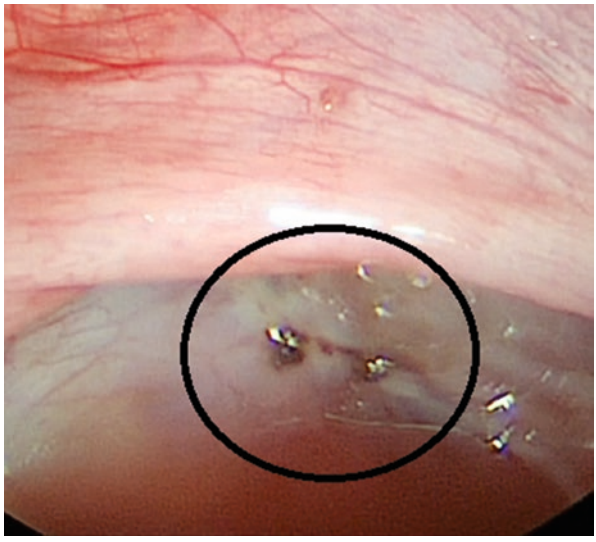

Fig. 43.4 Endometriosis of the peritoneum

endometriosis. Endometriosis in adolescents has been reported in some series up to 70% [1–12]. Surgeons should either biopsy it or remove the lesion, if possible, according to their level of experience, or call for an intraoperative consultation from a gynecology colleague to assist with the procedure.

This chapter will address complications of endoscopic surgery in adolescents, with attention paid to how to prevent such complications (e.g., access complications) and how to identify and manage them. The management of incidental findings during laparoscopy for endometriosis in adolescent patients will also be addressed.

Preoperative Preparation and Patient Positioning

Preoperative preparation is very important, especially when the patient has been suffering from chronic abdominal and pelvic pain [12]. The procedure, benefits, risks, and possible complications should be clearly explained, and informed consent should be obtained. The age of consent and the designation of emancipated adolescent vary in different states and different countries, although it is commonly around 18 to 19 years of age. In cases when patients cannot sign consent, the informed consent for surgery and other invasive procedures needs to be obtained from the legal guardian, most commonly their parents. The informed consent and the discussion should include the possibility of converting to open surgery and other possible complications.

When colonic involvement is suspected and possible colonic resection anticipated, most surgeons prefer mechanical bowel preparation the night before surgery. This issue has been controversial; the author prefers a simple mechanical bowel preparation without oral or systemic antibiotics the night before surgery.

Preparation of the operative field should include the vagina with gentle irrigation with antiseptic solution in cases where vaginal examination and uterine manipulation is necessary [12, 13]. Antibiotic surgical prophylaxis is very important, and it has been recommended by the Centers for Disease Control and Prevention for the prevention of surgical site infection. The author routinely uses it in all procedures. Antibiotic administration should be properly documented by the anesthesiologist and mentioned during the time-out procedure. Antibiotic prophylaxis for surgery is given within 1 hour prior to surgical incision, except for vancomycin which is administered within 2 hours of surgical incision. Intraoperative re-dosing is necessary during procedures that exceed two half-lives of the drug to maintain adequate serum and tissue concentrations. Postoperative antibiotic administration is not recommended in clean and clean-contaminated procedures [12–17].

Positioning of the patient on the operating room table is important. Most patients are operated in the lithotomy position. Pressure points need to be properly padded, with the arms generally tucked in. This can create pressure points or damage to fingers, especially if the operating room table needs to be moved from Trendelenburg to reverse Trendelenburg or side-to-side positions [12, 13]. The patient should be properly strapped to the operating room table in order to prevent accidental fall or malposition of the patient during surgery. Deep vein thrombosis prophylaxis is important, especially in obese patients or when a long procedure is anticipated. Obese patients with a body mass index over 30 may have significant comorbidities, including metabolic disorders and cardiopulmonary problems. Other risk factors include duration of surgery over 4 hours, hypotension, and prolonged steep Trendelenburg position [18–21].

Close communication with the anesthesiologist is essential. Preoperative planning and evaluation should address the surgery planned, comorbidities, coagulation problems, and issues pertaining the effects of pneumoperitoneum. Anesthesiologist and surgeon should be aware of the significant physiological changes during

laparoscopic surgery. Pneumoperitoneum can cause mechanical effects by elevating the diaphragm and also by decreasing venous return to the heart. The effects of CO_2 can cause significant hypercarbia with acidosis and cardiac arrhythmias, including premature ventricular contractions, ventricular tachycardia, and even ventricular fibrillation. Increased intra-abdominal pressure can cause vagal stimulation resulting in bradyarrhythmias. It is important to reduce the intra-abdominal pressure to less than 12 mm Hg [18–21]. It is also important to remember some of these patients may be debilitated and may have been suffering with chronic pain. Many of them may have been subjected to long-term analgesics, including opioid use that could result in addiction.

The management of postoperative pain control and analgesia should be discussed. Appropriate and effective postoperative pain control is essential for a positive postoperative recovery. Laparoscopic procedures cause less tissue trauma and are associated with less postoperative pain. It has been reported that up to 80% of adult patients require postoperative opioids following laparoscopy. The number may be higher in adolescents with chronic pelvic pain that have received preoperative opioids [18–21]. Oral analgesics can be used if the patient's gastrointestinal tract is functional. The use of local preemptive anesthesia with bupivacaine is effective. It should be used before the incisions are made and the trocars are placed. Analgesia can also be achieved with the use of intravenous and rectal acetaminophen and ketorolac if there is no bleeding contraindication.

Pain from laparoscopy can originate from nociceptive stimuli from the trocar access, laparoscopic incisions, or conversion to open surgery. This must be kept in mind. The pain can also originate from the peritoneum or abdominal viscera. Epidural infusions and the use of patient-controlled analgesia with morphine are very common techniques to control pain, especially following intestinal surgery. Other techniques used include intrathecal opioids and wound catheter infusion [18–21].

The use of four quadrant transversus abdominis plane block (TAP) and continuous posterior TAP analgesia has gained significant popularity [22–24]. The author has used TAP block frequently in adolescent patients undergoing laparoscopic surgery. TAP block has facilitated postoperative recovery and ambulation. In the author's clinical experience, TAP block decreases the need for postoperative opioids. It is even more important in patients with chronic pelvic pain. TAP blocks do not effectively cover incisions placed at or above the T10 dermatome. They are also not effective to control visceral pain and may require additional opioid analgesia [22–24]. The anesthesiologist needs to talk to the patient and guardian before the operation to explain the procedure and to obtain informed consent.

Postoperative shoulder pain can cause significant distress to the patient. Although the mechanism is unclear, it is most often considered to be a referred pain caused by irritation of the diaphragm and stretching of the phrenic nerves. There are many maneuvers described to try to minimize postoperative shoulder pain. These maneuvers include lowering the pneumoperitoneum pressure; warming and humidifying the CO_2 gas; instillation of normal saline; intraperitoneal irrigation with local anesthetic solution (lidocaine and bupivacaine); and, probably the most effective one, trying to remove as much CO_2 gas after the procedure is completed. The surgeon should avoid

rushing to remove the ports before as much gas as possible is evacuated. Patience is important to maximize removal of the CO_2, and it may be beneficial to place the patient in Trendelenburg position for a few minutes while the lower ports are opened. There are studies demonstrating significantly less postoperative shoulder pain in patients who had maneuvers to remove as much gas as possible [25–30].

Laparoscopic Access and Complications

Most access-related mortality in laparoscopic surgery is due to vascular or gastrointestinal injuries. Deaths have also been caused by air embolism during insufflation. It has been reported that up to 50% of major complications in laparoscopy occur during access. This figure has remained practically the same during the last 25 years [12, 13, 18, 31–34]. It is extremely stressful and worrisome to start an operation with a complication of access. After dealing with a complication that can be life-threatening, the surgeon still has to complete the planned operation, convert to an open procedure, or have to postpone the surgery to come back another day to solve the original indication for the operation (Fig. 43.5).

The advantages of laparoscopy over laparotomy have been well established throughout the literature. Besides all the known advantages, the risk of minor complications after gynecological surgery has been reported to be 40% lower with

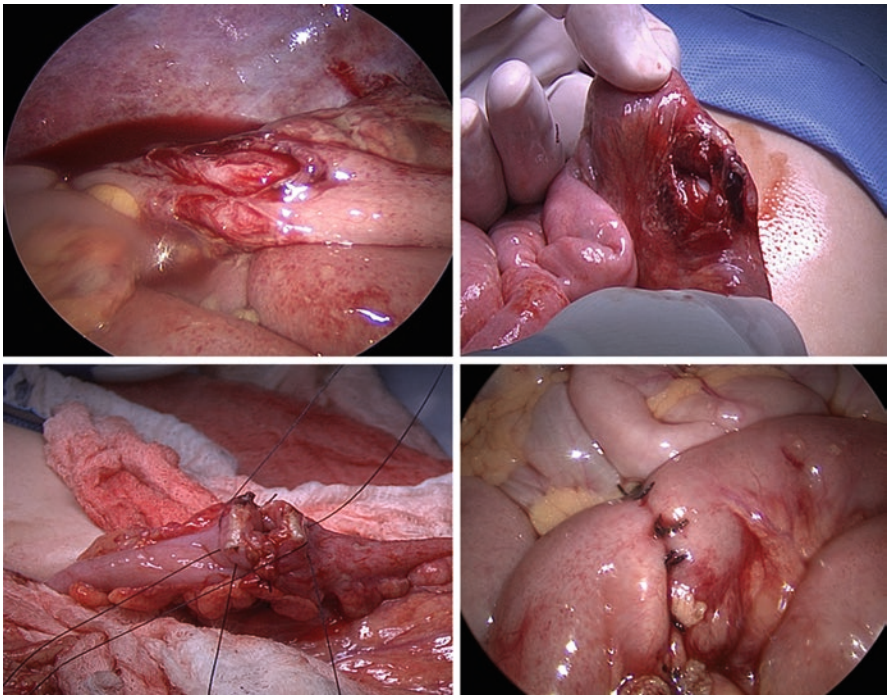

Fig. 43.5 Intestinal perforation converted to open laparotomy

laparoscopy than with laparotomy. The risk of major complications is similar and comparable. The reported overall risk of all complications is 8.9% with laparoscopy and 15.2% with laparotomy. Despite the possible complications, laparoscopy is a safe technique with an overall low incidence of complications. Access-related injuries occur in less than 1% of patients [31–35].

There are a variety of access techniques to enter the abdominal cavity. No single technique is free of complications or better and more reliable than others. Complications including fatalities have been reported with practically all entry techniques. The safest technique to access depends on the surgeon's experience and expertise. The presence of comorbidities and other factors can make access more difficult. Some of these factors include previous surgery (especially midline laparotomy), body habitus, obesity, umbilical hernia repair, and peritoneal adhesions. The learning curve or using a different technique or instruments for the first time may be another risk factor. Even an experienced surgeon using a new technique for the first time should be considered inexperienced, similar to an experienced pilot flying a new aircraft for the first time [36].

There are basically three entry techniques: the Veress needle, the open technique (Hasson), and various direct trocar entries. There are many variations of these techniques. The Veress needle has been traditionally the preferred approach by gynecologists. The Veress needle also has different variations, including an optical Veress needle [31–35] (Fig. 43.6). As a historical note of interest, the first Veress needle was designed and named after internist Jànos Veres; it was originally used to produce iatrogenic pneumothorax to treat patients with tuberculosis. The Veress needle technique in laparoscopy was popularized by Raoul Palmer [37].

The trocar first techniques include direct trocar insertion without pneumoperitoneum, optical trocars, shielded disposable trocars, radially expanding trocars, and reusable trocarless visual access cannula. In addition, there are many other laparoscopic techniques that have gained popularity, including mini-laparoscopy with 2- and 3-mm trocars, single incision surgery (SIS), and natural orifice transluminal endoscopic surgery (NOTES). There are many variations of single incision surgery

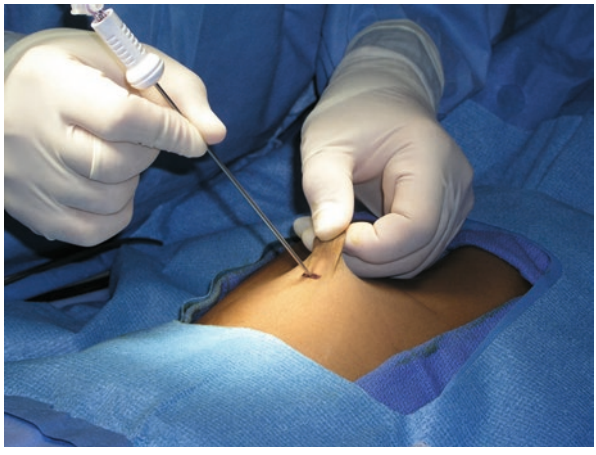

Fig. 43.6 Veress needle entry

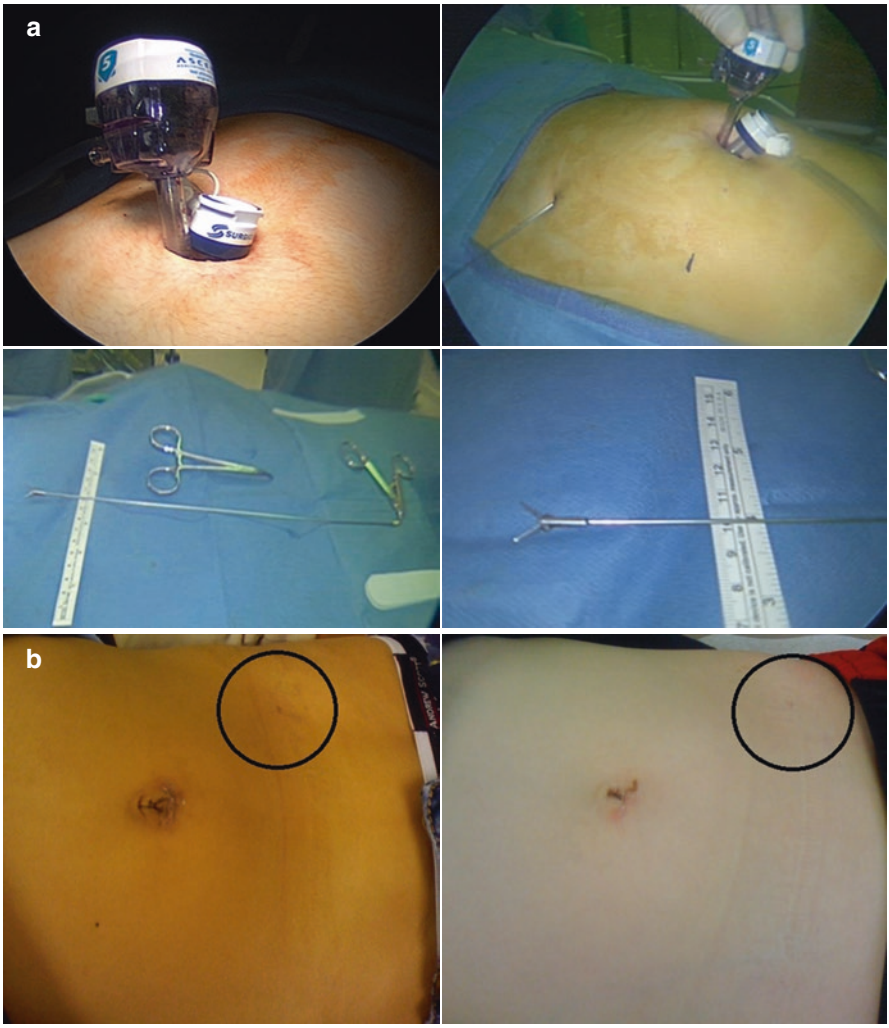

Fig. 43.7 (**a**) Stringel single incision with mini forceps. (**b**) Stringel single incision postoperative picture. Mini alligator forceps scars illustrated with circles

with a variety of names and abbreviations, including SILS (single incision laparoscopic surgery), single port access (SPA), and laparoendoscopic single site surgery (LESS)—just to mention some, with new terms and acronyms appearing frequently. There is no consensus about the nomenclature and no universally accepted terminology [31–35, 37, 38] (Figs. 43.7a, b and 43.8a–c).

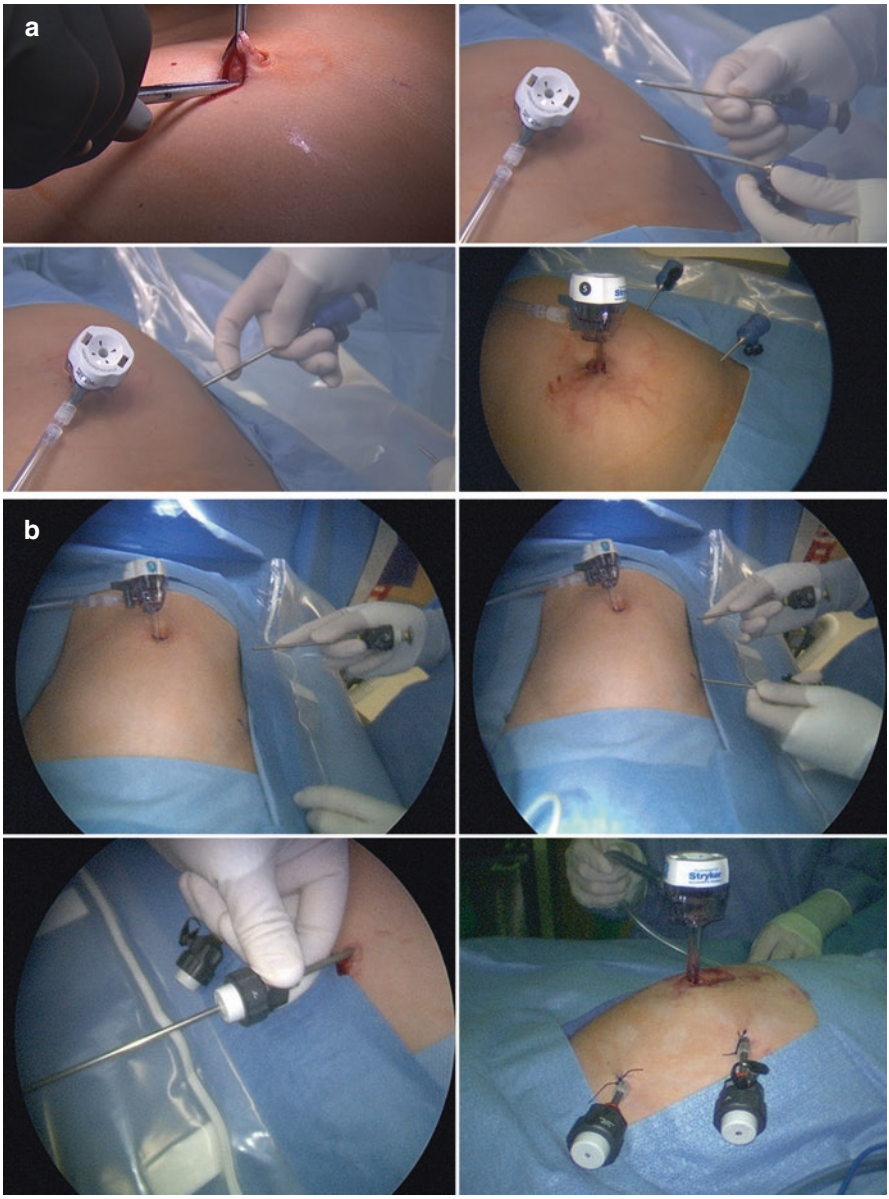

Fig. 43.8 (**a**) Mini-laparoscopy CareFusion™ set. (**b**) Mini-laparoscopy Storz ™ set. (**c**) Mini-laparoscopy postoperative scars

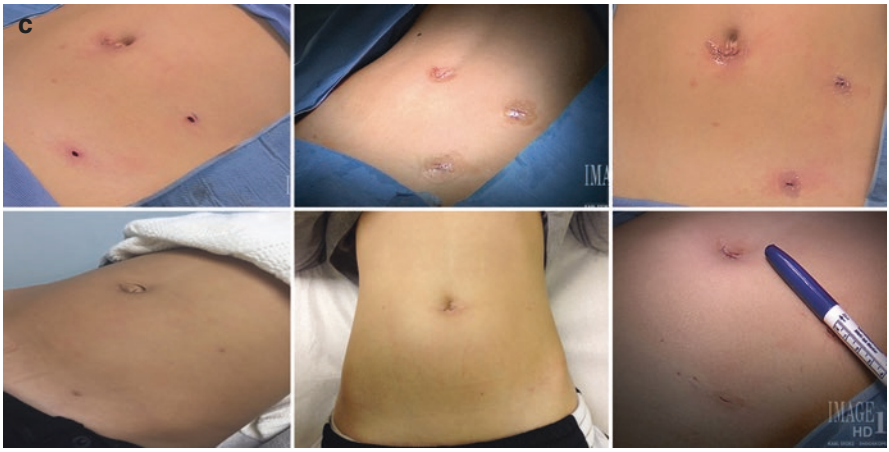

Fig. 43.8 (continued)

The author effectively uses a direct trocar entry similar to the one described by Nezhat [35]. This entry entails the following steps: make a small incision below the umbilicus; expose the root of the umbilicus or umbilical stalk and grasp it with a Kocher clamp; pull the abdominal wall forward to elevate it; and make a small midline incision in the fascia and dissect bluntly with a mosquito clamp. The entry to the peritoneum can be felt securely most times with the mosquito clamp; subsequently, a blunt trocar is inserted. This technique is especially useful in obese patients. The port is held securely with the tip of the index finger positioned 2–3 cm from the tip to have absolute control and to prevent sudden and uncontrolled peritoneal entry. When the access is difficult, a similar technique with a visual trocar entry is effective. Occasionally, the port enters the falciform ligament, and insufflation of this structure can make entry more difficult. The author has not seen any complications in more than 1000 cases since this technique was adopted several years ago, except for occasional minor bleeding and falciform ligament and abdominal wall insufflation without any consequences. It is essential to carefully inspect the peritoneal cavity to rule out injuries (Figs. 43.9a, b and 43.10).

There are many other entry anatomical areas. One of the most popular is the left upper quadrant approach, as described by Palmer [37] (Fig. 43.11). The approach can be done with Veress needle, direct trocar entry, visual trocar entry, and other techniques. The right upper quadrant has also been used, but sometimes the liver can be injured. Gynecologists have used the transuterine and trans-cul-de-sac approach for creation of pneumoperitoneum. The ninth or tenth intercostal space approach has also been used successfully [12, 31–35]. The author has also used a direct right or left lower quadrant direct approach, making a small incision and doing a muscle-splitting dissection until the peritoneum can be grasped with mosquito clamps.

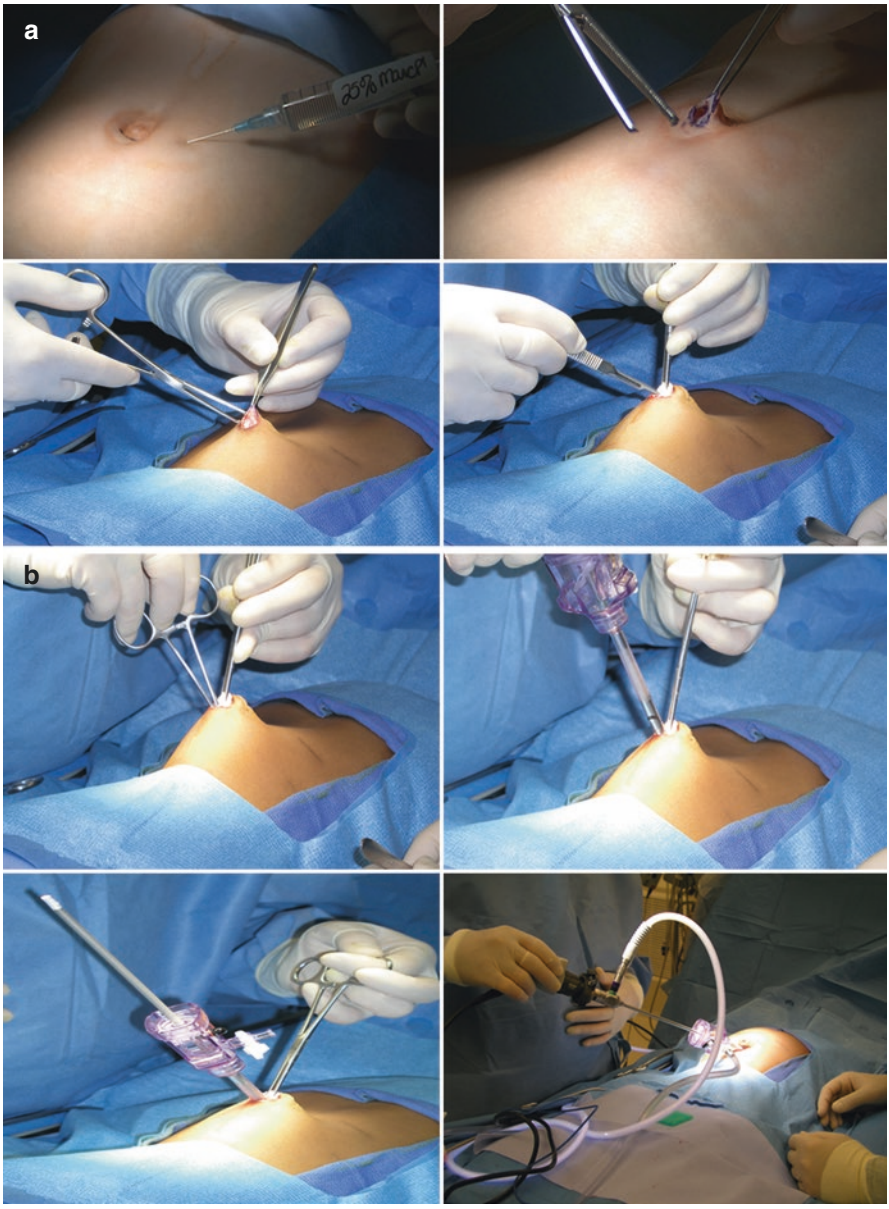

Fig. 43.9 (**a**) Trocar first entry technique. (**b**) Trocar first entry technique follow-up

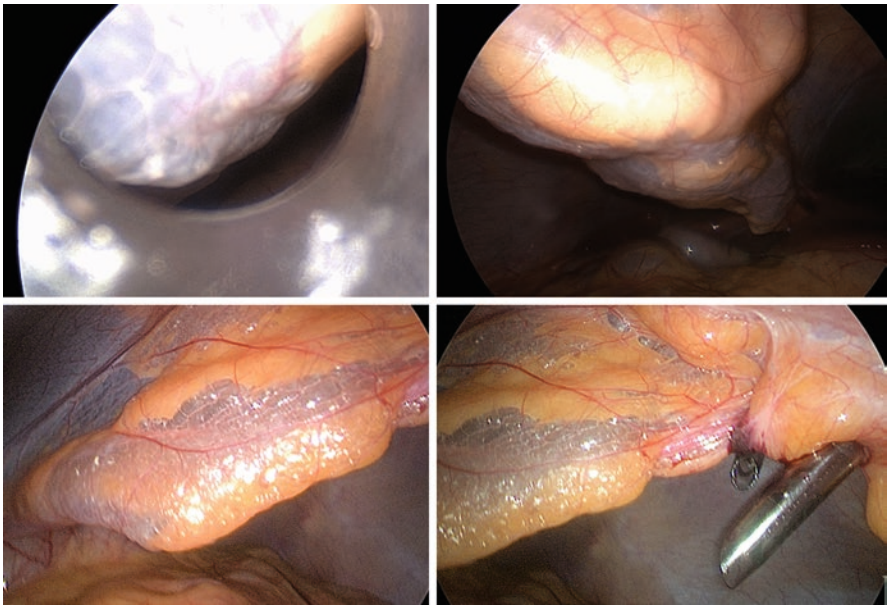

Fig. 43.10 Umbilical ligament insufflation

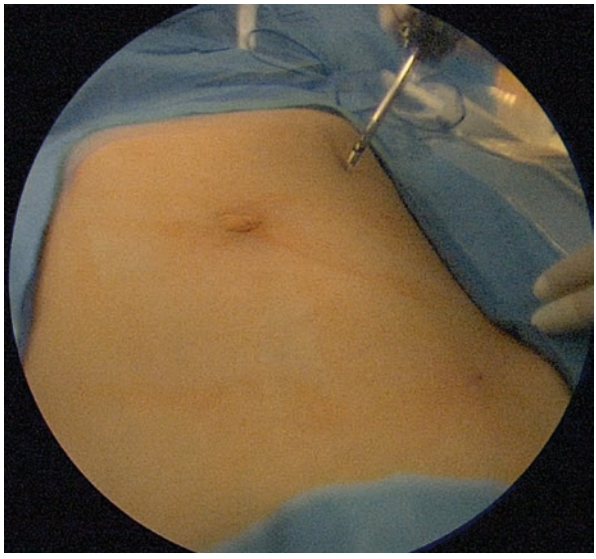

Fig. 43.11 Palmer's point entry

A small incision is made in the peritoneum and a blunt port introduced directly into the peritoneal cavity. After pneumoperitoneum is established, the secondary ports can be introduced under direct vision. This approach may require upsizing the port from 5 to 10 mm to prevent CO_2 leak or placing a large suture to prevent losing pneumoperitoneum.

The bladder and stomach should be decompressed before port placement. The anesthesiologist should place a nasogastric or orogastric tube to remove air and liquid from the stomach. This is especially important during emergency or urgent procedures, or when the patient has been forcefully ventilated by mask before intubation, which can introduce a significant amount of air in the stomach and proximal small bowel and contribute to access injuries. Placement of a urinary catheter is important to reduce bladder injuries and facilitate pelvis surgery. In some institutions, a preoperative bladder ultrasound with a portable ultrasound device is utilized to evaluate the need for a Foley catheter. Ultrasonography is only applicable in short laparoscopic procedures, mainly those performed in the upper abdomen or simple appendectomies. It is not practical for pelvic laparoscopy [39].

The placement of secondary ports is important, as injuries with secondary port placement are also possible. Significant bleeding can occur from injury to the inferior epigastric vessels or other abdominal wall vessels (Fig. 43.12). The placement

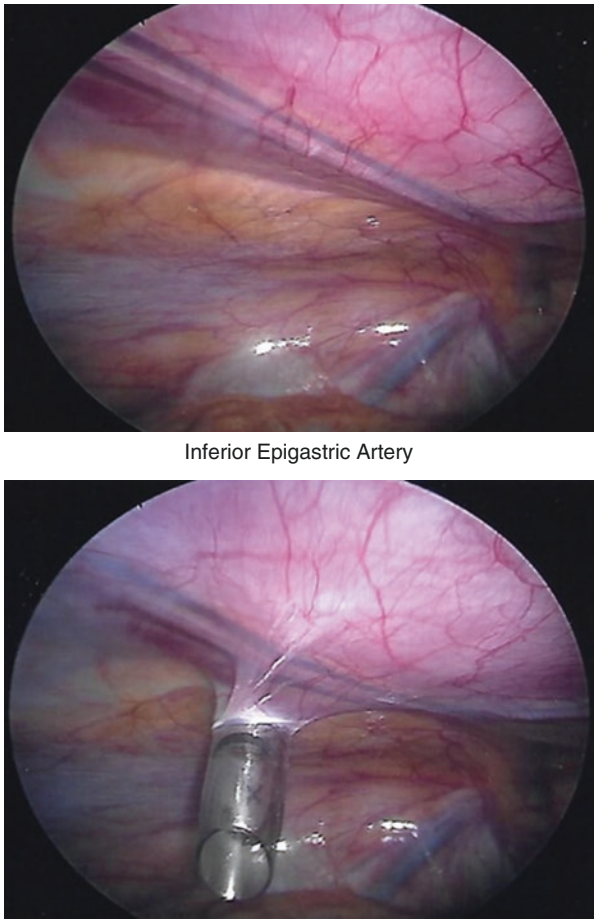

Fig. 43.12 Inferior epigastric vessels. Nearly missed by secondary trocar

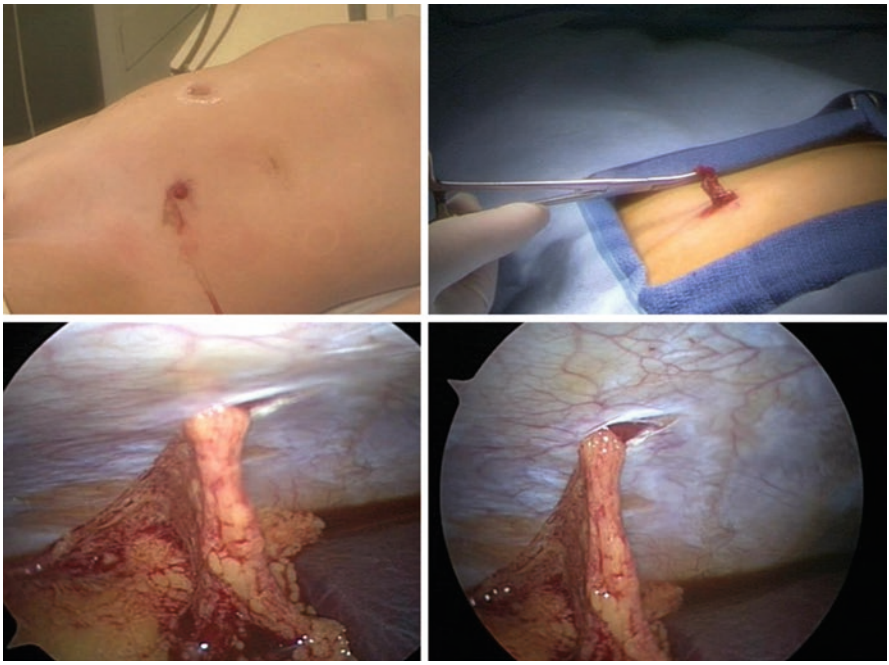

Fig. 43.13 Omental evisceration

of secondary trocars should be always done under direct visualization. The port placement depends on the type of surgery contemplated. Generally, triangulation is preferred, especially if laparoscopic suturing is anticipated. As a general rule, 5-mm or smaller (mini-laparoscopy) ports do not need to be closed except in small or skinny adolescents. It is important to close 10- and 15-mm ports to prevent hernias. The use of single port and single approach laparoscopy has been reported to have more trocar hernias than conventional laparoscopy [40] (Fig. 43.13).

Access Complications

The incidence of abdominal access injuries has been reported to be 5% to 30% in 10,000 laparoscopic procedures. The overall estimated mortality of laparoscopic entry has been reported to be 1 in 100,000 procedures. Vascular and intestinal injuries amount to approximately 76% with a great number of bowel injuries (10–50%) unrecognized for over 24 hours [12, 13, 18, 31–35, 41]. Vascular injuries are usually obvious, especially when major arteries or veins are involved. However, most injuries involve minor vessels. The reported rate of vascular injuries has ranged from 0.1 to 6.4 per 1000 laparoscopic procedures [42–46].

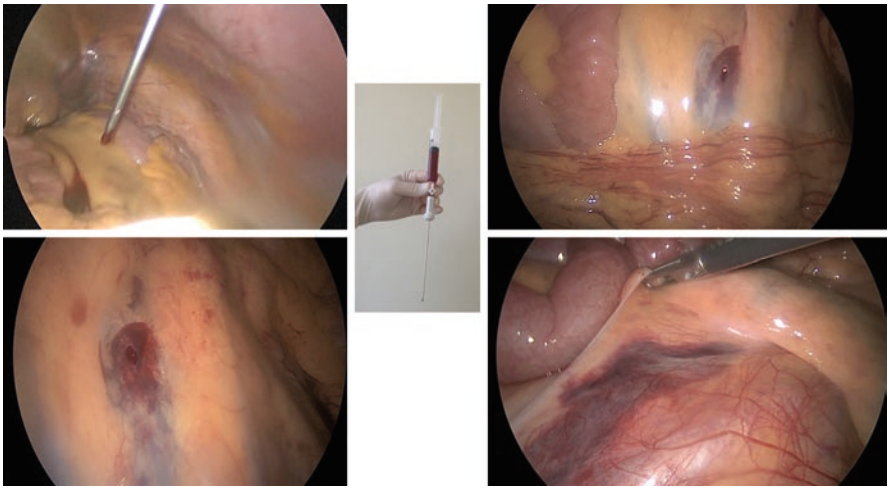

Fig. 43.14 Veress needle injury to retroperitoneum

Injury to major vessels such as the aorta, vena cava, and iliac veins will produce rapid and massive blood loss. It needs immediate attention and communication with the anesthesiologist for immediate resuscitation and blood transfusion. The rapid transfusion protocol for hypovolemic hemorrhagic shock should be immediately activated. The gynecologist or operating surgeon should call for help. It is especially useful to have trauma or vascular surgeons available to assist since they are familiar in managing patients with major hemorrhage (Fig. 43.14). Control of bleeding is essential and may often necessitate applying trauma management principles, such as damage control laparotomy, including open abdomen and second-look laparotomy [47, 48]. The need to convert to open procedure depends on the amount and rate of blood loss, the presence of hypovolemic shock, the inability to identify the source of bleeding, and the experience and expertise of the laparoscopic surgeon. The author teaches residents that converting to an open procedure is often good judgment and not a complication.

In a reported survey, the incidence of vascular injuries was iliac artery (19%), iliac and retroperitoneal veins (9%) (Fig. 43.15), mesenteric vessels (7%), aorta (6%), inferior vena cava (4%), and liver (2%) [49]. A comprehensive analysis of 622 trocar injuries reported 408 injuries to major vessels, 30 abdominal wall hematomas, and 182 other injuries (mainly intestinal injuries). Mortality was largely attributed to aorta and inferior vena cava injuries. In 10% of the series, gastrointestinal injuries had delayed presentation and diagnosis, resulting in 21% mortality [50].

Minor vascular injuries can occur with laceration of the mesentery or omentum. The inferior epigastric vessels can bleed profusely, obscure the operative field, and delay the operation, though rarely require conversion to an open procedure. The

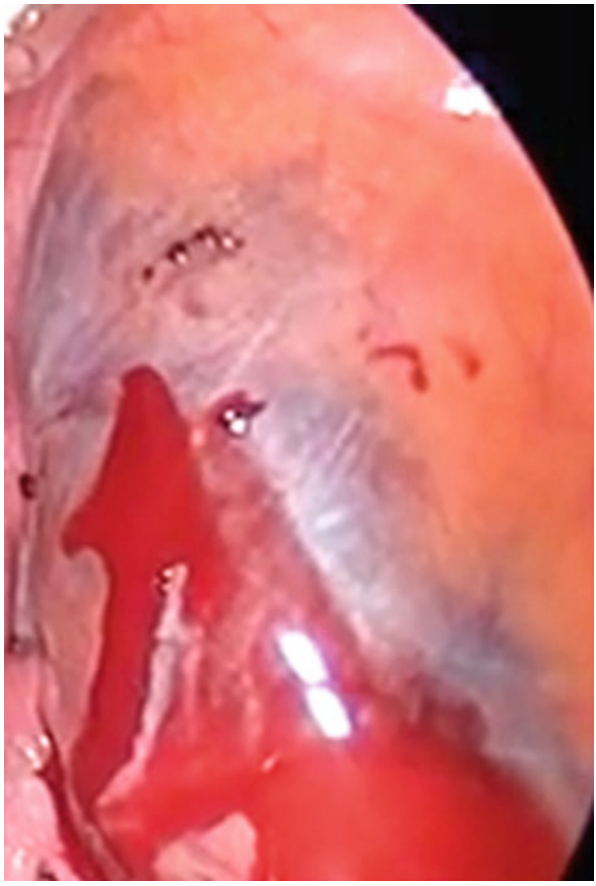

Fig. 43.15 Iliac vein injury. It resolved with pressure

epigastric and other abdominal wall vessels may not bleed during the procedure because of the tamponade effect of the pneumoperitoneum or the pressure from the trocar. These vessels may have delayed bleeding or a hematoma after the pneumoperitoneum is released or the trocars are removed (Fig. 43.16a, b).

A useful maneuver to control significant bleeding from inferior epigastric or abdominal wall vessels is to introduce a Foley catheter, inflate the balloon, and create tamponade by pulling on the catheter. This maneuver may allow temporary control of the bleeding until a definite strategy is used to manage the hemorrhage (Figs. 43.17 and 43.18). Numerous types of fascial closure devices are available to control bleeding with a figure-eight suture.

Gastrointestinal injury can cause significant morbidity and mortality. It is considered the third cause of death after anesthesia and vascular injuries. Approximately 30% to 50% of intestinal injuries are caused by laparoscopic access [51–54]. Gastrointestinal injuries can generally be managed effectively when diagnosed early during the laparoscopic procedure (Fig. 43.19a, b), especially by experienced

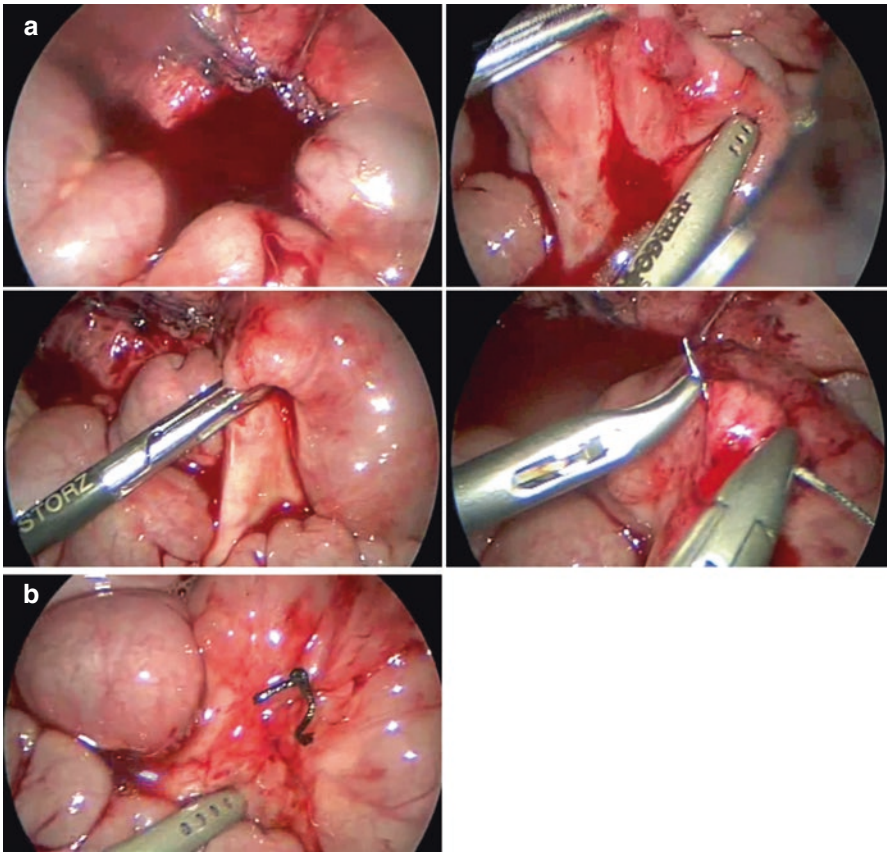

Fig. 43.16 (**a**) Mesenteric injury with secondary trocar. (**b**) Mesenteric injury with secondary trocar controlled with one suture

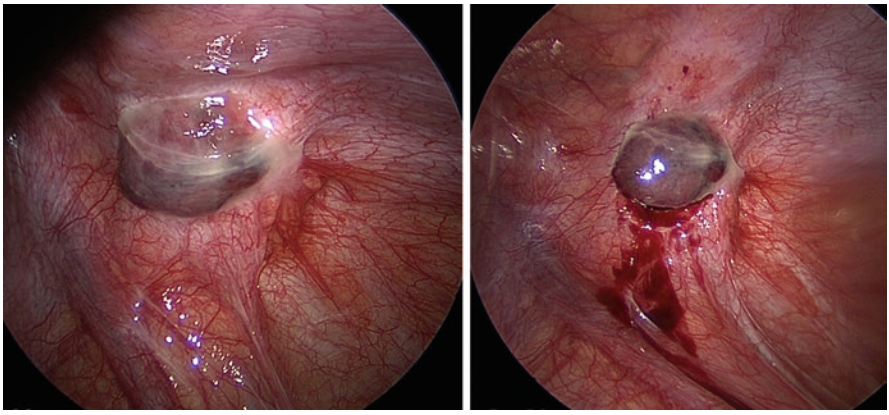

Fig. 43.17 Abdominal wall hematoma

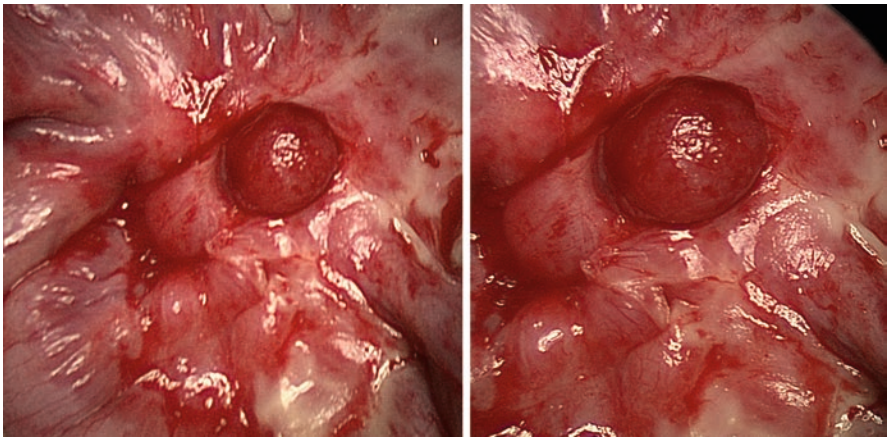

Fig. 43.18 Mesenteric hematoma

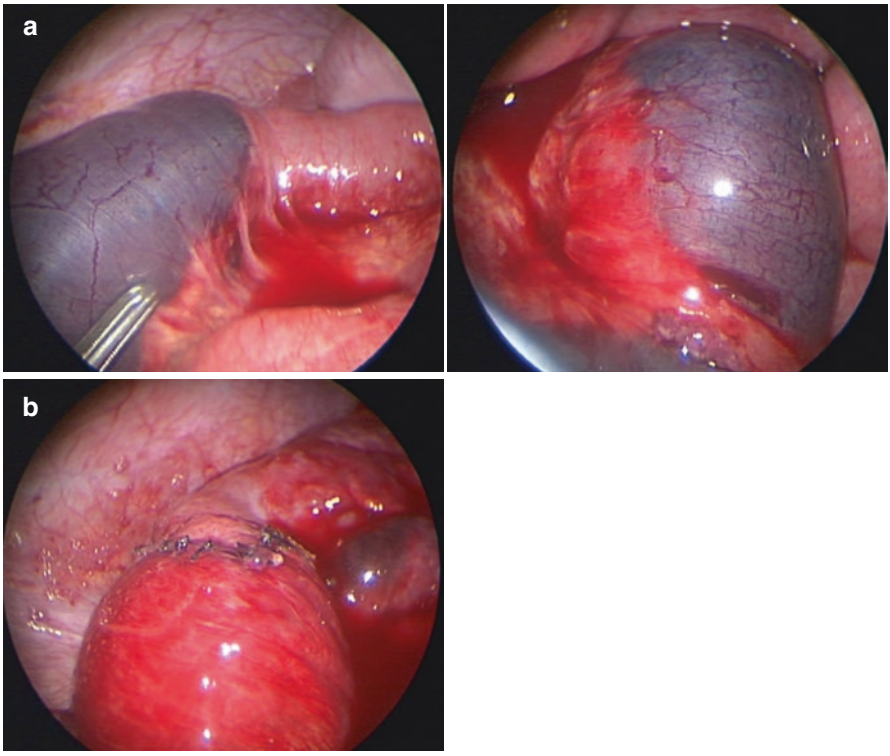

Fig. 43.19 (**a**) Intestinal hematoma. (**b**) Intestinal hematoma ruptured. It was repaired with sutures. Patient discharged home in 5 days

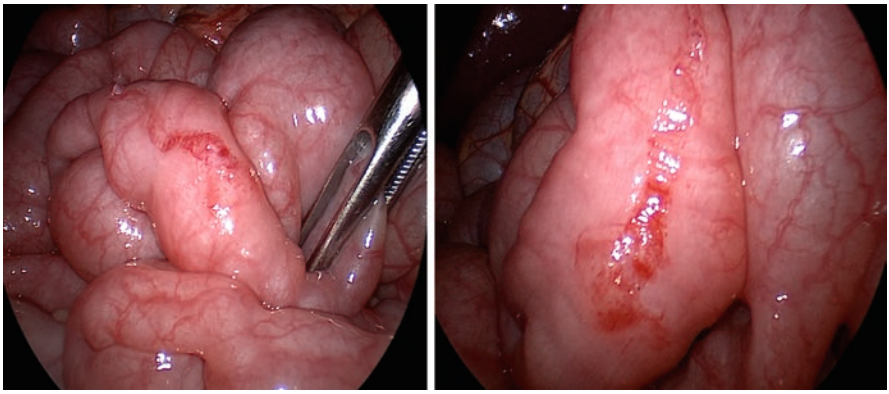

Fig. 43.20 Serosal tear

laparoscopic surgeons. The problem with intestinal perforations is that they are often difficult to diagnose and may also have a delayed presentation. This has also been observed following blunt abdominal trauma. Most often the gastrointestinal injury is caused by the laparoscopic access. However, intestinal perforations can be secondary to the use of energy, lysis of adhesions, and bowel manipulation [55] (Fig. 43.20).

It is extremely important to carefully and methodically examine the intestine after establishment of the pneumoperitoneum, especially when entry is difficult and even in uncomplicated easy laparoscopic access procedures. The presence of excessive fluid in the abdomen, especially bilious or succus entericus, mandates careful and thorough gastrointestinal examination. Gastrointestinal perforations are more common in patients with intestinal adhesions and previous surgery. They have been reported with all different access techniques, and in some series the open (Hasson) technique had higher percentage of bowel perforation than closed (Veress) approach [54].

The most important factor to prevent complications or even death from intestinal perforations is to recognize them early, preferably during the laparoscopic procedure. Most of the injuries can be readily repaired without any serious consequences. The injury should be repaired in cases when there is questionable viability of the tissue, such as significant serosal tears and energy damage to the intestine (Figs. 43.21 and 43.22). Some of these injuries may present late with peritonitis and sepsis. It is also important to maintain a high level of suspicion when the postoperative course is complicated. The presence of excessive pain, abdominal distension, signs of peritonitis, unexplained fever, and persistent peritoneal fluid and free air demand a careful search to exclude intestinal perforation (Figs. 43.23a–c and 43.24).

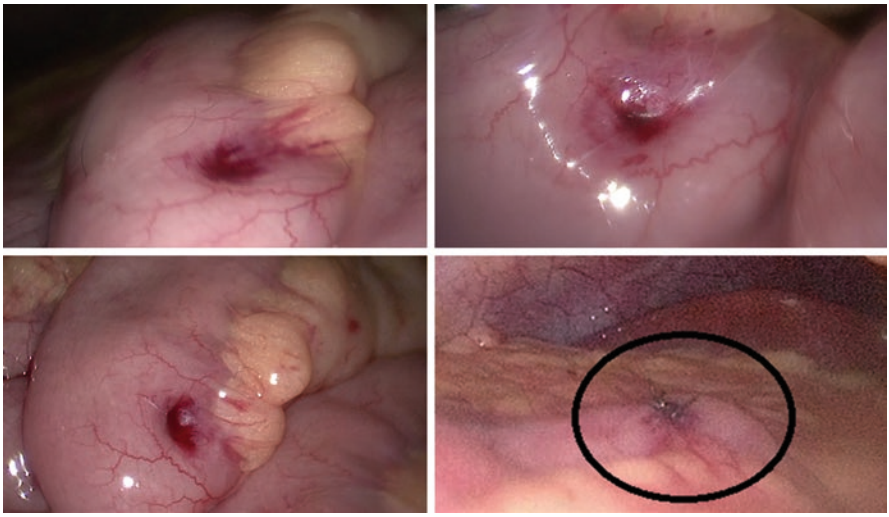

Fig. 43.21 Trocar injury to intestine

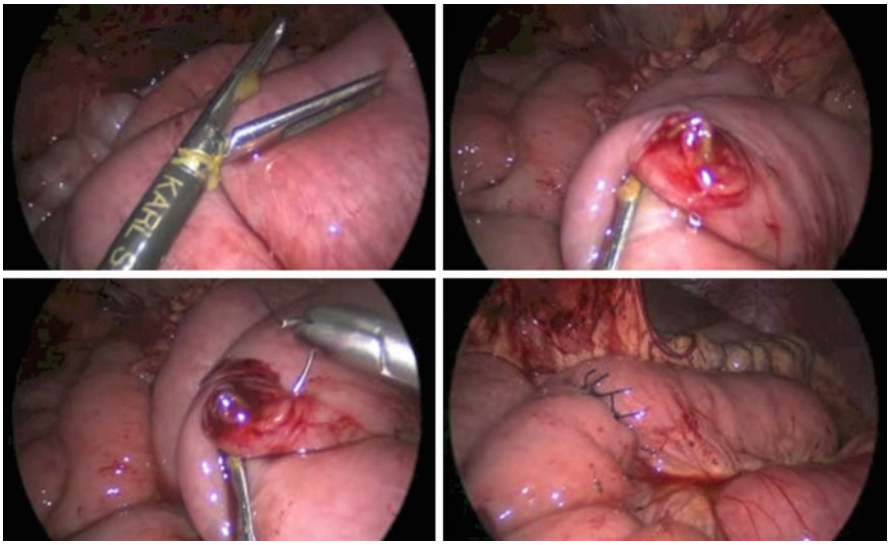

Fig. 43.22 Intestinal perforation repaired laparoscopically

Bladder injuries are rare, especially when effective bladder decompression has been done with a Foley catheter in place. A large series of 136,997 patients reported eight bladder injuries, four of which were caused by the Veress needle, two by the primary trocar entry, and two by the secondary trocar [55]. It has been recommended that Veress needle punctures or small laceration do not need repair. Larger lacerations can be repaired with absorbable sutures in two layers. Most repairs can be done laparoscopically. Laparoscopic suturing of the bladder is generally easily accomplished by most experienced laparoscopic surgeons. A Foley catheter should remain in place to drainage for 4–10 days according to the degree of the perforation. When in doubt, a urologist should be consulted for immediate advice and follow-up.

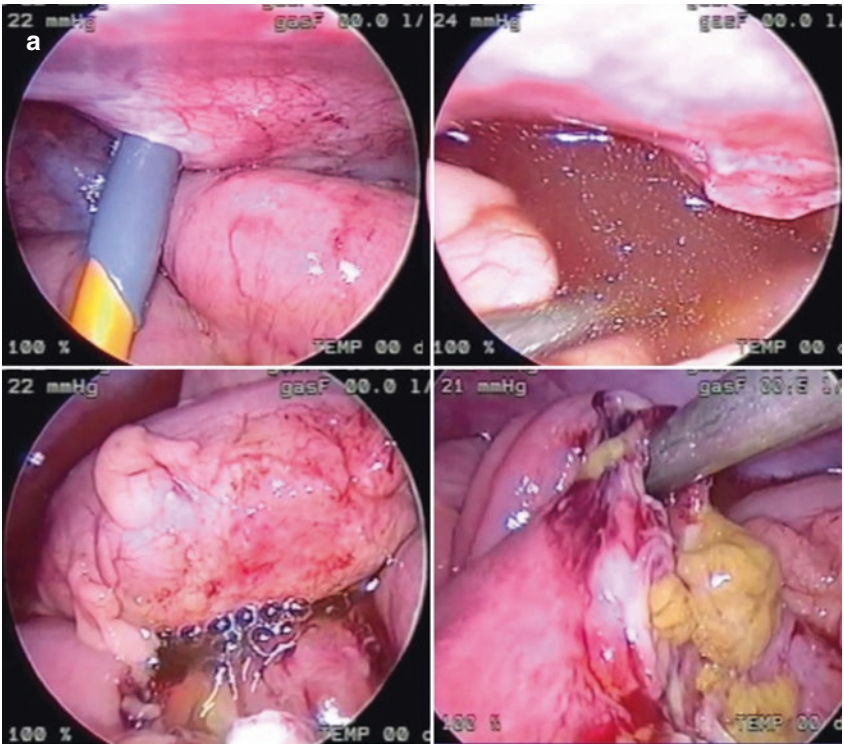

Fig. 43.23 (**a**) Delayed presentation of intestinal perforation. (**b**) Debridement of intestinal perforation. (**c**) Intestinal perforation repaired laparoscopically with interrupted sutures. Patient recovered uneventfully and was discharged home 7 days later

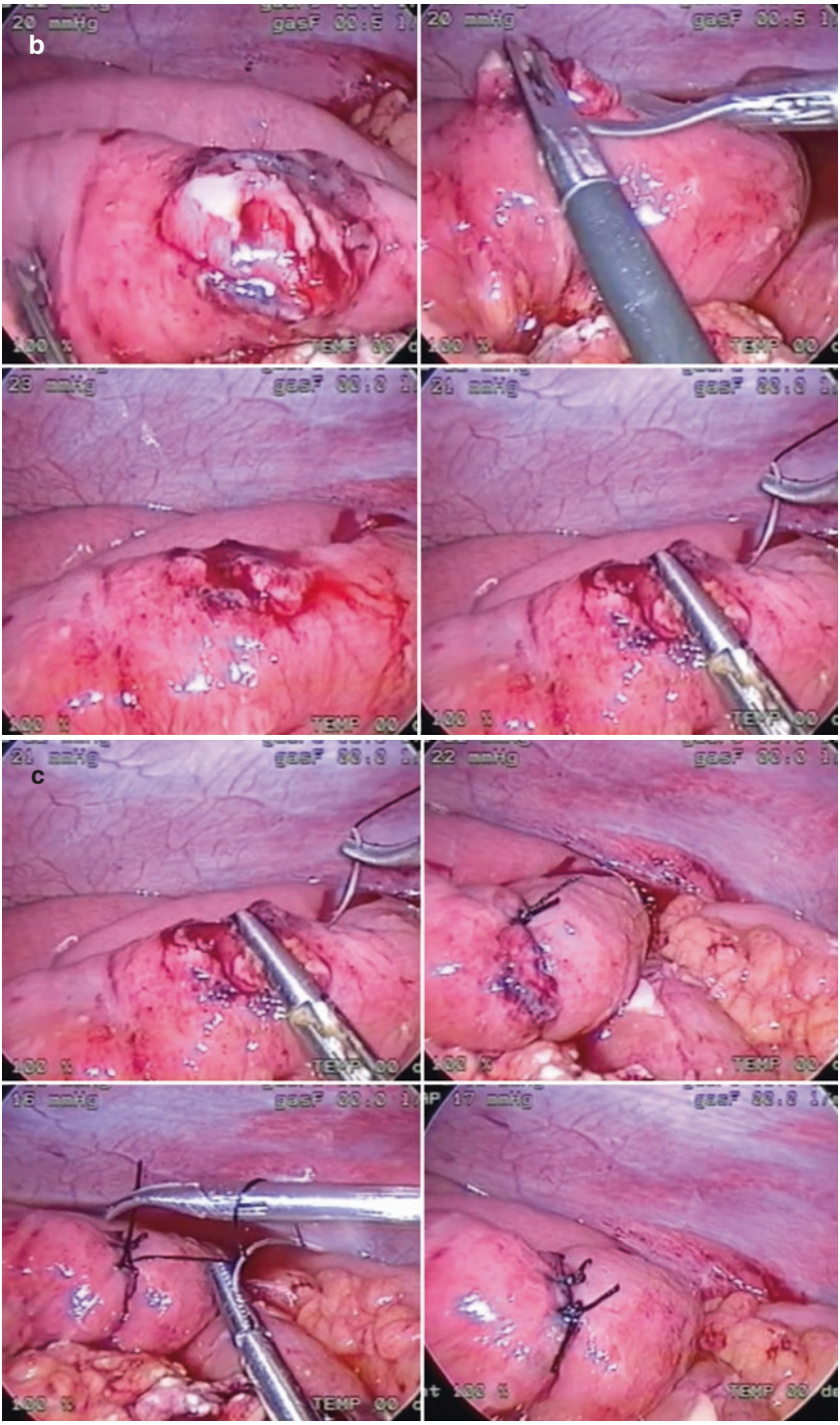

Fig. 43.23 (continued)

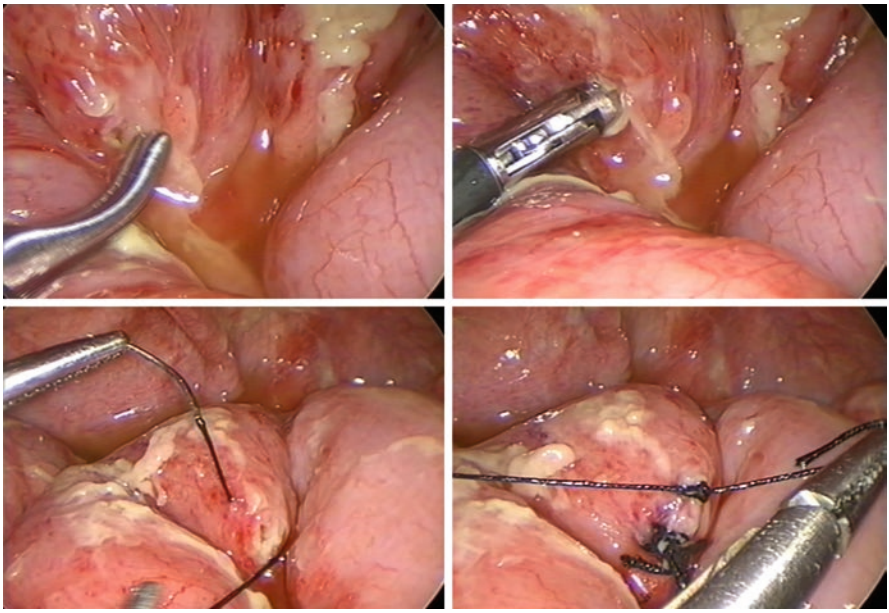

Fig. 43.24 Delayed presentation of intestinal perforation with peritonitis. Successfully repaired by laparoscopy. Patient recovery was uneventful, discharged home 7 days postoperatively

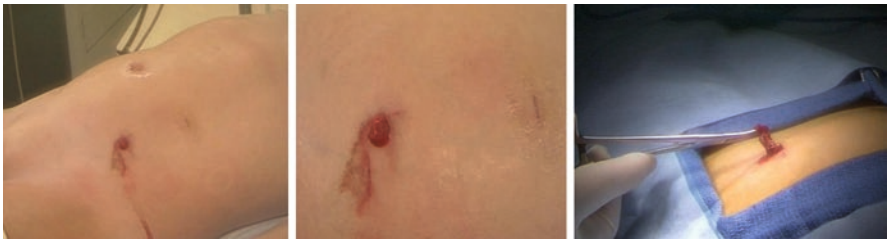

Fig. 43.25 Omental evisceration through a 5-mm port site

It is important to inspect the abdominal cavity before releasing the pneumoperitoneum. Sometimes the intestine or omentum can be sutured to the port during closure. The omentum can sometimes adhere or protrude through the trocar site and needs to be released [56] (Figs. 43.25, 43.26, and 43.27a–c). The incidence of wound infection is rare, especially when perioperative antibiotics are administered. The umbilicus must be cleaned thoroughly before placement of the umbilical port or Veress needle.

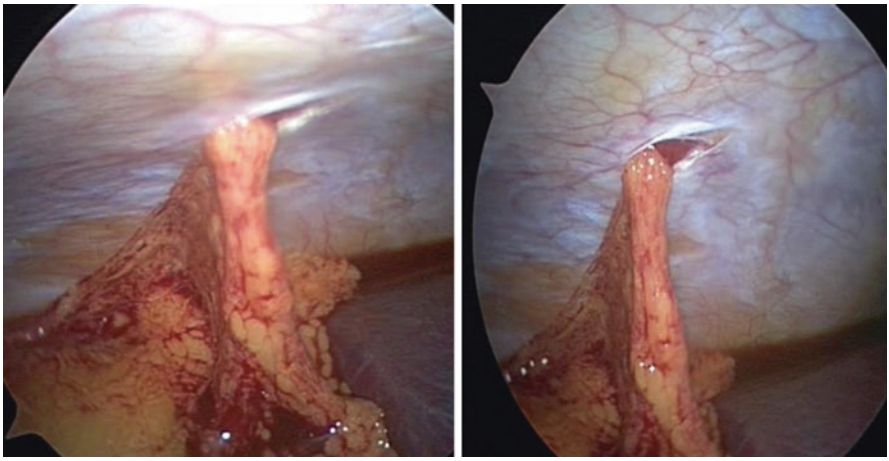

Fig. 43.26 Omental hernia

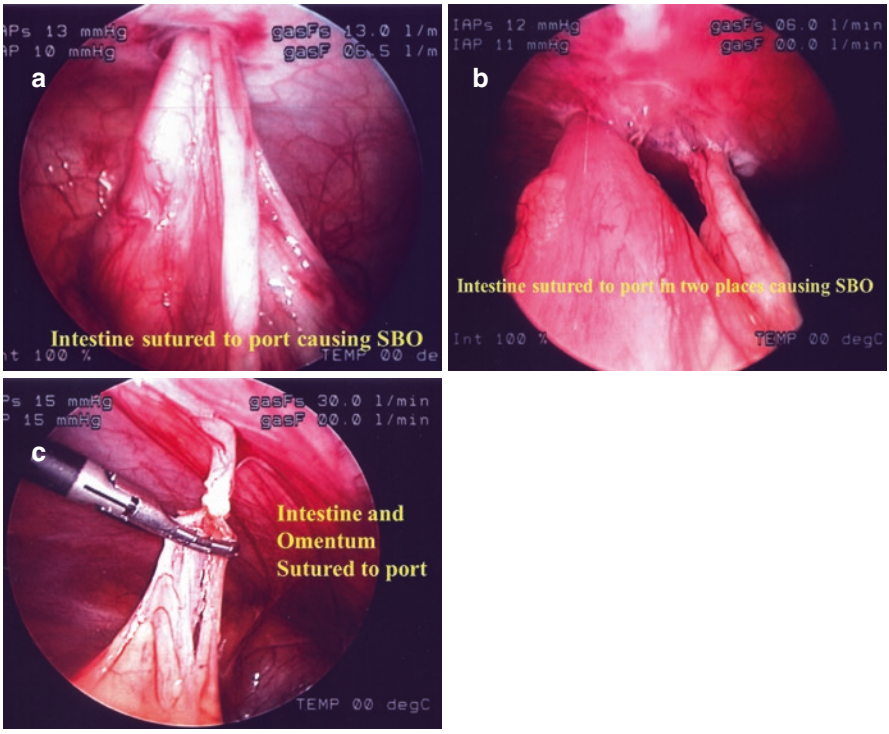

Fig. 43.27 (**a**) Intestine sutured to port presenting with small bowel obstruction. (**b**) Intestine sutured to two different ports causing small bowel obstruction. (**c**) Intestine and omentum sutured to port site

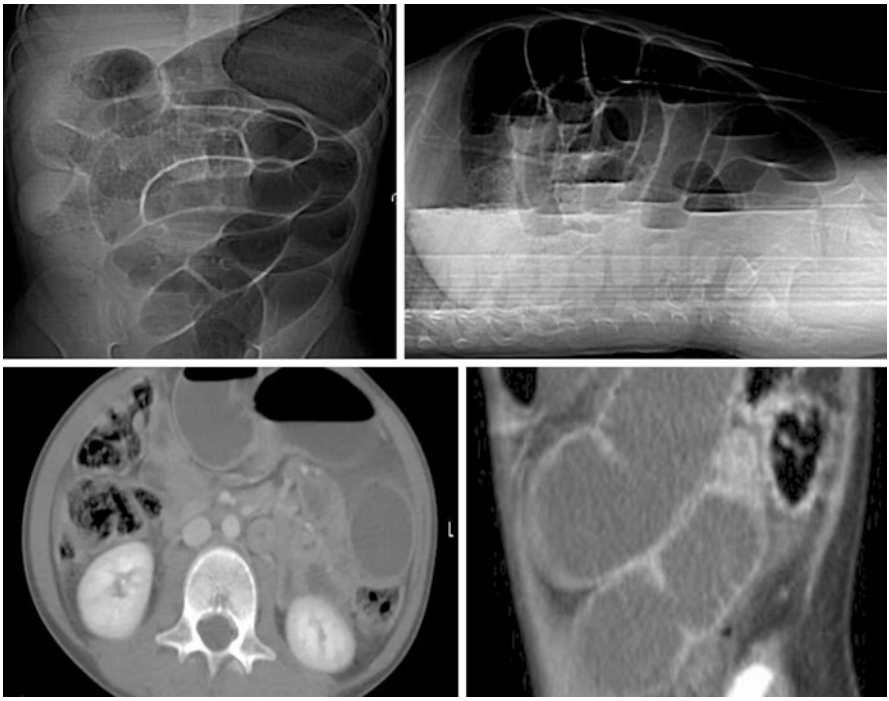

Fig. 43.28 Small bowel obstruction caused by adhesions

Peritoneal Adhesions

Peritoneal adhesions have been the subject of extensive discussion in the surgical literature. Adhesions are the most common cause of intestinal obstruction (60–75%) (Fig. 43.28). They are the most common complication of abdominal and pelvic surgery. They also are reported to cause infertility and chronic abdominal pain. The presence of adhesions can increase the operative time in both laparoscopy and laparotomy. In addition, they can add to morbidity because of intestinal damage. Indeed, they are one of the most common causes of reoperation [57–62]. The etiology, classification, prevention, and management of adhesions have been a topic of controversy among gynecologists and surgeons.

Endometriosis can be associated with peritoneal and especially pelvic adhesions.

Laparoscopy has been reported to decrease the formation of adhesions in both clinical and experimental studies compared with laparotomy. Midline laparotomy has been reported to have a 50% incidence of umbilical adhesions compared to 1.6% following laparoscopy [57–62] (Fig. 43.29). There are proponents of performing diagnostic laparoscopy and lysis of adhesions in all patients with chronic pelvic pain. Other authors feel that routine lysis of adhesions does not help alleviate chronic pelvic pain. The incidence of chronic pelvic pain has been reported to affect

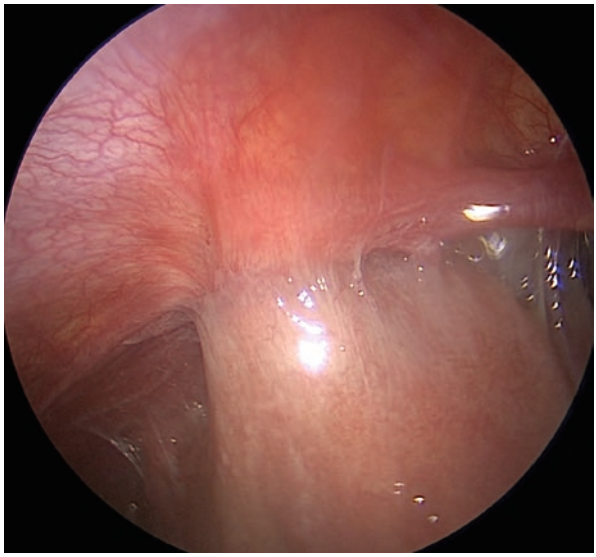

Fig. 43.29 Umbilical adhesions

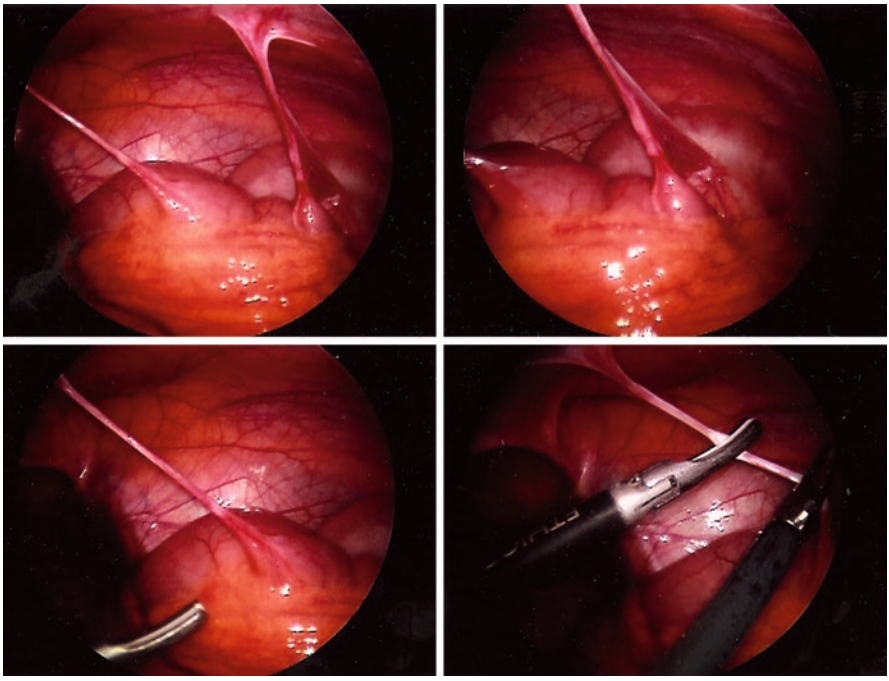

Fig. 43.30 Umbilical and pelvic adhesions

38 per 100 women, very similar to lower back pain (41 per 1000) [57–62]. The management of pelvic adhesions in females with chronic pelvic pain continues to be controversial and the subject of future studies (Fig. 43.30).

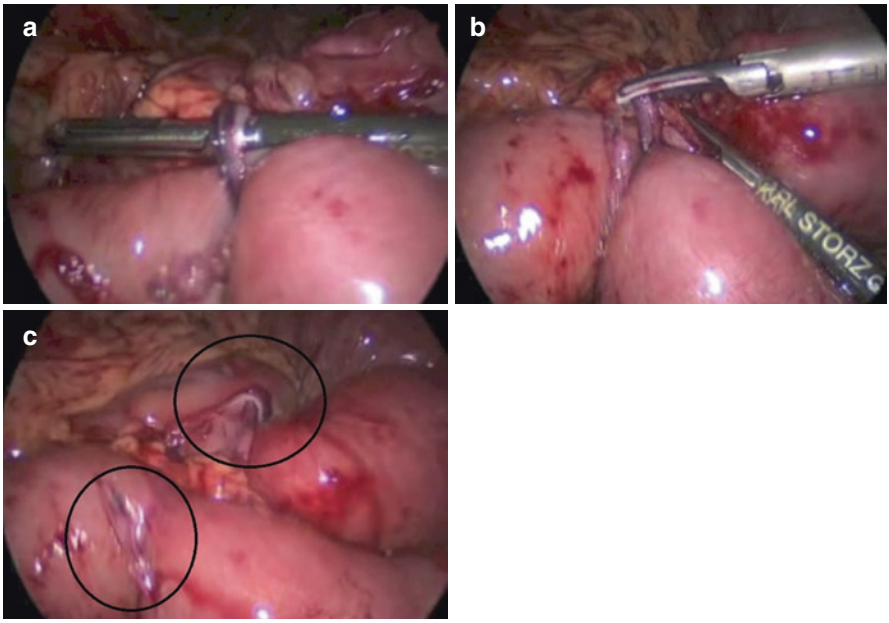

Fig. 43.31 (**a**) Small bowel obstruction caused by a single band (adhesion). (**b**) A single band causing small bowel obstruction divided with Harmonic Scalpel™. (**c**) A single band (adhesion) divided. Small bowel obstruction resolved. Divided band illustrated by circles

Lysis of adhesions is certainly indicated to relieve small bowel obstruction or when it is obvious that a large adhesion may cause problems (Fig. 43.31a–c). General and pediatric surgeons often have to manage patients with small bowel obstruction and have to perform extensive lysis of adhesions. Lysis of adhesions in the presence of small bowel obstruction with a very distended intestine can be challenging and requires laparoscopic experience and expertise (Figs. 43.32a–c and 33a, b). The author, who has had significant experience performing laparoscopy in patients with small bowel obstruction, instructs residents that they can always convert to open laparotomy. He never hesitates to convert to open if he anticipates a very long procedure, and if the patient is unstable, does not tolerate the pneumoperitoneum, or there is bleeding, necrotic bowel, or a confusing anatomy. He generally tries to find collapsed bowel. The distended bowel is difficult to manipulate, as it may be inflamed and can rupture easily. Thus, he divides the bands or adhesions that are causing the obstruction. Caution is advised because extensive lysis of adhesions in the presence of distended bowel may be difficult and hazardous (Fig. 43.34a–c).

There are several studies that demonstrate the benefit of laparoscopy for reducing trauma, viscera manipulation, and decreasing postoperative adhesion formation. Other studies have questioned the clinical impact of the reduction of postoperative adhesions [57–62]. The author often scrubs with adolescent

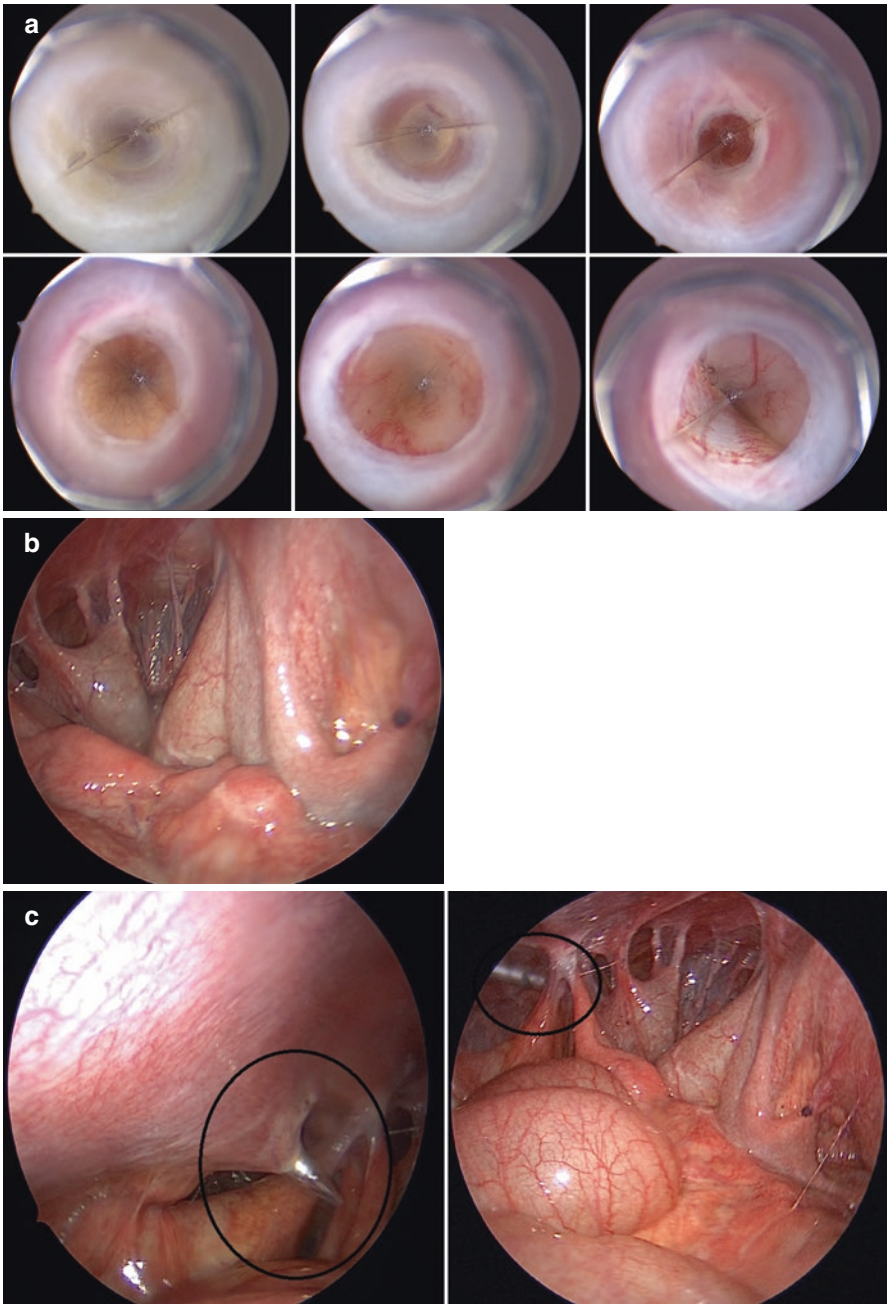

Fig. 43.32 (**a**) A sequential picture of visual trocar entry at Palmer's point in a patient with critical closed loop small bowel obstruction caused by adhesions from previous surgery. (**b**) Same patient as (**a**) after successful visual trocar entry. View of extensive adhesions from Palmer's point. (**c**) Same patient as (**a**), secondary trocars placement illustrated by circles. Small bowel obstruction resolved with extensive laparoscopic lysis of adhesions

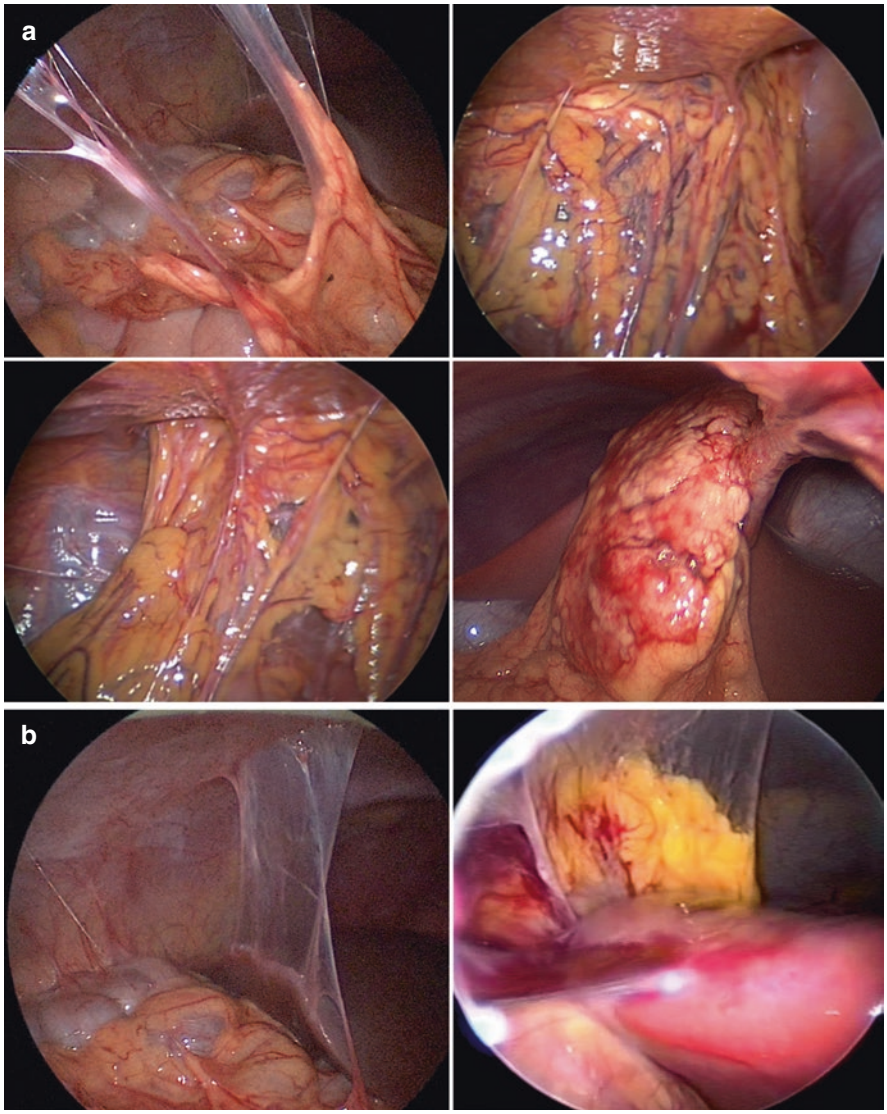

Fig. 43.33 (**a**) Omental adhesions. (**b**) Liver adhesions

gynecologist colleagues to assist with extensive lysis of adhesions, especially in the presence of chronic pelvic pain and endometriosis. He defers to their experience and expertise to the extent of lysis of pelvic adhesions indicated in that particular clinical situation. In his personal experience with diagnostic laparoscopy in the management of children with chronic recurrent abdominal pain,

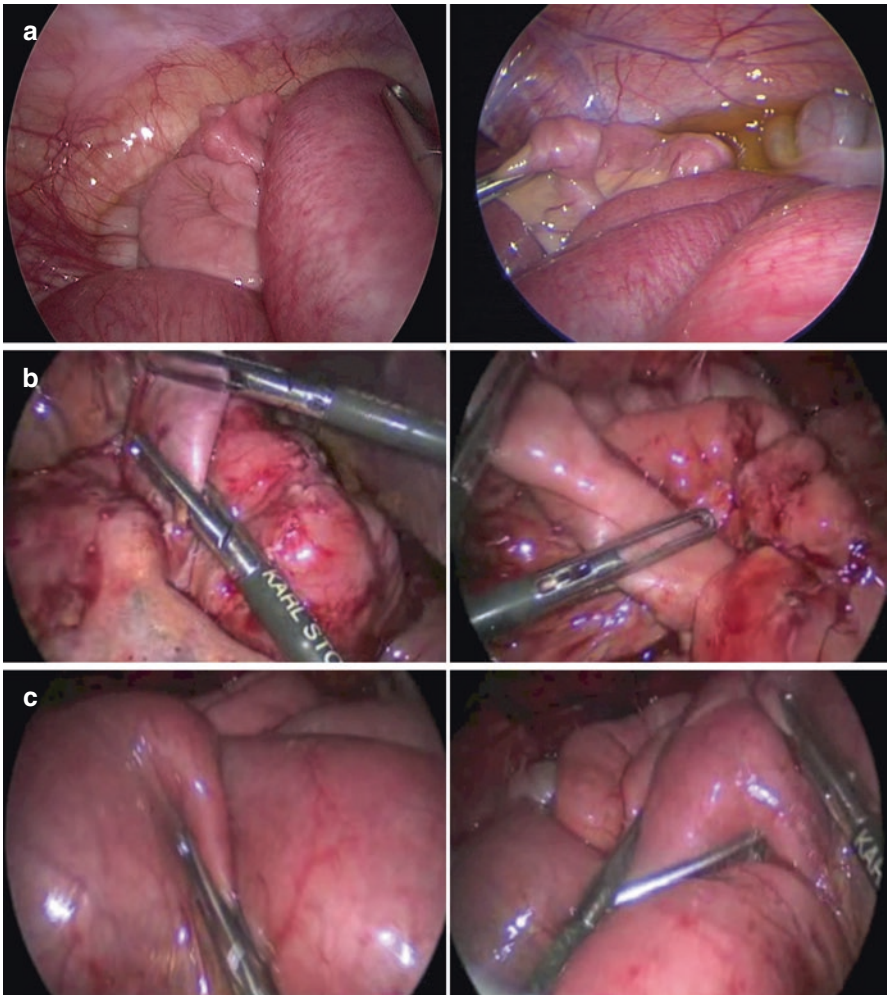

Fig. 43.34 (**a**) Collapsed distal small bowel compared to proximal distended obstructed small bowel in a patient with small bowel obstruction. (**b**) Running distal collapsed small bowel toward distended proximal intestine searching for the area of obstruction. (**c**) Excessive manipulation of distended obstructed proximal small bowel can cause bowel injuries and immediate or delayed perforation

pathological findings were found that could explain the pain in 12 of 13 patients, and five of those patients had significant cecal adhesions. Similar experience has been reported in the literature [60, 63] (Fig. 43.35).

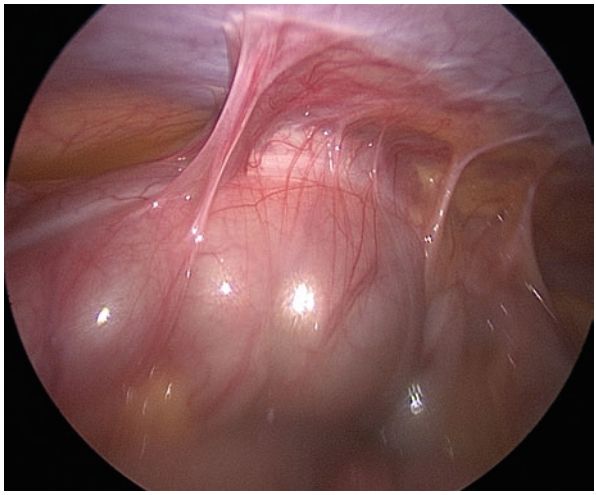

Fig. 43.35 Cecal adhesions

Meckel's Diverticulum

Meckel's diverticulum is a remnant of the omphalomesenteric duct, also known as the vitelline duct. It is a true diverticulum since it contains all the layers of small bowel. It is located in the antimesenteric border of the ileum. Its incidence has been reported in 2% to 4% of the population and in 1.2% of autopsies. Traditionally, Meckel's diverticulum has been characterized by the so-called rule of 2s: it occurs in 2% of the population; it is located 2 feet from the ileocecal valve; it is generally 2 inches long and has a 2-cm diameter; and it contains two types of ectopic tissue (gastric and pancreatic) and has a 2:1 male-to-female ratio. Heterotopic tissue may also be duodenal, colonic, and endometrial [64, 65]. Meckel's diverticulum commonly presents in the pediatric population or young adults. The most common presentations in order of frequency are bleeding (30–56%), small bowel obstruction (14–42%), and diverticulitis (6–14%). Other presentations include a Littre hernia, malignancy, perforation, intussusception, and, as described in isolated case reports, endometriosis in the diverticulum [66–71].

The treatment of complicated Meckel's diverticulum is excision. Some surgeons recommend segmental intestinal resection. The author manages most cases with simple laparoscopic diverticulectomy by stapling the diverticulum transversally across the intestine. Occasionally, he performs a segmental resection when the base of the diverticulum or adjacent small bowel is compromised. There is controversy about managing a Meckel's diverticulum found incidentally. The overall lifetime clinical complication rate is 4% to 6%. Some authors against elective removal of incidentally found Meckel's diverticulum argue that a large number of diverticula need to be removed to prevent one death (800 diverticulectomies). Other authors recommend removal of all Meckel's diverticulum [72–74]. The main issue is the morbidity caused by complications of Meckel's diverticulum and not the mortality. Mortality is extremely rare even in cases with severe complications.

The author recommends removal of a Meckel's diverticulum found during diagnostic laparoscopy for abdominal and pelvic pain [64, 67, 68, 71]. When a diverticulum is found during laparoscopy for removal of endometriosis, the diverticulum should be removed unless there are other issues such as complicated or extensive surgery that prevent the removal. The finding of a Meckel's diverticulum should be carefully documented in the operative report, and the patient and family should be informed. The family should be informed if the incidentally found diverticulum is being removed or told the reason why it is not removed (Fig. 43.36).

The author always runs the terminal ileum and small bowel during diagnostic laparoscopy and also in cases of uncomplicated appendicitis. He also has incidentally found a diverticulum while removing a complicated appendix. Under this circumstance, he is careful to document the finding and explain it to the patient and family. He gives them the option to have it removed later or to leave it alone. Most patients and/or families prefer to have it removed. When removal is delayed, he generally returns to the operating room in 2–3 months to perform a laparoscopic diverticulectomy. No complications to date have occurred with this approach. It is possible that in some cases of chronic abdominal and pelvic pain, Meckel's diverticulum may play a role in the symptomatology (Fig. 43.37). Laparoscopy is also

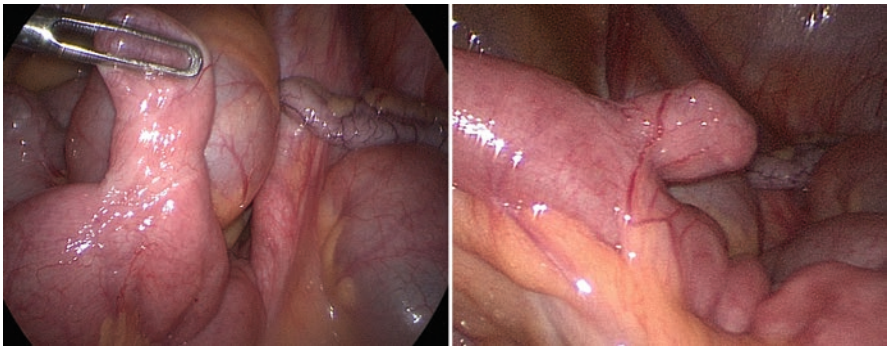

Fig. 43.36 Incidentally found Meckel's diverticulum removed at a second laparoscopic surgery 6 weeks later

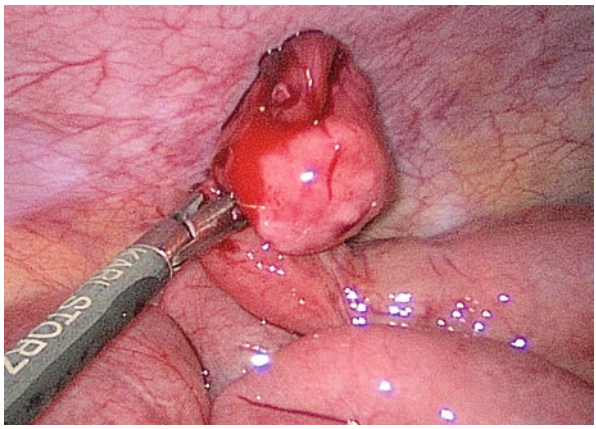

Fig. 43.37 Inflamed Meckel's diverticulum. Removed by laparoscopy

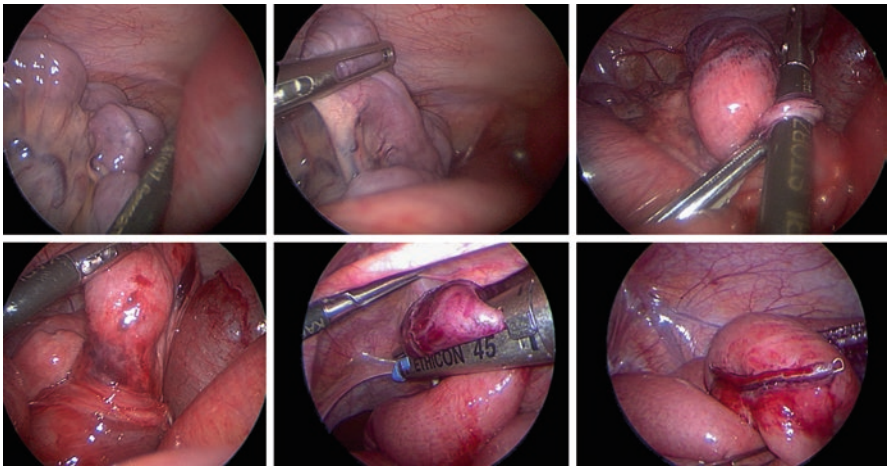

Fig. 43.38 Meckel's diverticulum causing small bowel obstruction removed by laparoscopy

safe and effective in the management of complicated Meckel's diverticulum, either by primary laparoscopic diverticulectomy or by laparoscopic-assisted removal or bowel resection (Fig. 43.38).

The Appendix

The pediatric and general surgeons are often requested to assist the gynecologist with laparoscopic appendectomy. The appendix plays an important role in the etiology of acute and chronic pain and sometimes may contribute to the symptoms [75–77]. It has been recommended that appendectomy should be performed during diagnostic laparoscopy for chronic abdominal and pelvic pain and in cases of endometriosis [12, 63, 75, 76]. The incidence of endometriosis of the appendix has been reported in several studies from 0.054% to 0.3% and 0.80% in large series of resected appendices. It can be as high as 50% in patients with pelvic endometriosis. In patients with gastrointestinal endometriosis, the appendix has been involved in 3% of the cases [12, 75–78] (Fig. 43.39a–d).

The appendix has been regarded as a vestigial organ. However, several recent studies report an important role of the appendix in the development and preservation of the intestinal immune system. The appendix contains a microbiota and commensal gut flora that plays a role in the healthy function of the intestine. This flora can be reintroduced into the colon in case of disease. Lack of the appendix predicts a worse outcome for recurrent *Clostridium difficile* infection [79, 80]. That said, the benefits of removing the appendix in patients with endometriosis and chronic pelvic pain definitely outweigh the risks of preserving it.

Laparoscopic appendectomy can be performed in the great majority of patients, even those with complicated appendicitis. There are several techniques of doing appendectomies. The appendiceal blood supply can be secured and divided with

energy devices, ligatures, clips, or a stapler. The base of the appendix can be double-tied with Vicryl Endoloop™, free ties, endoclips, or endostapler. There are no advantages of any particular technique. It depends on the preference and experience of the surgeon (Fig. 43.40a–c).

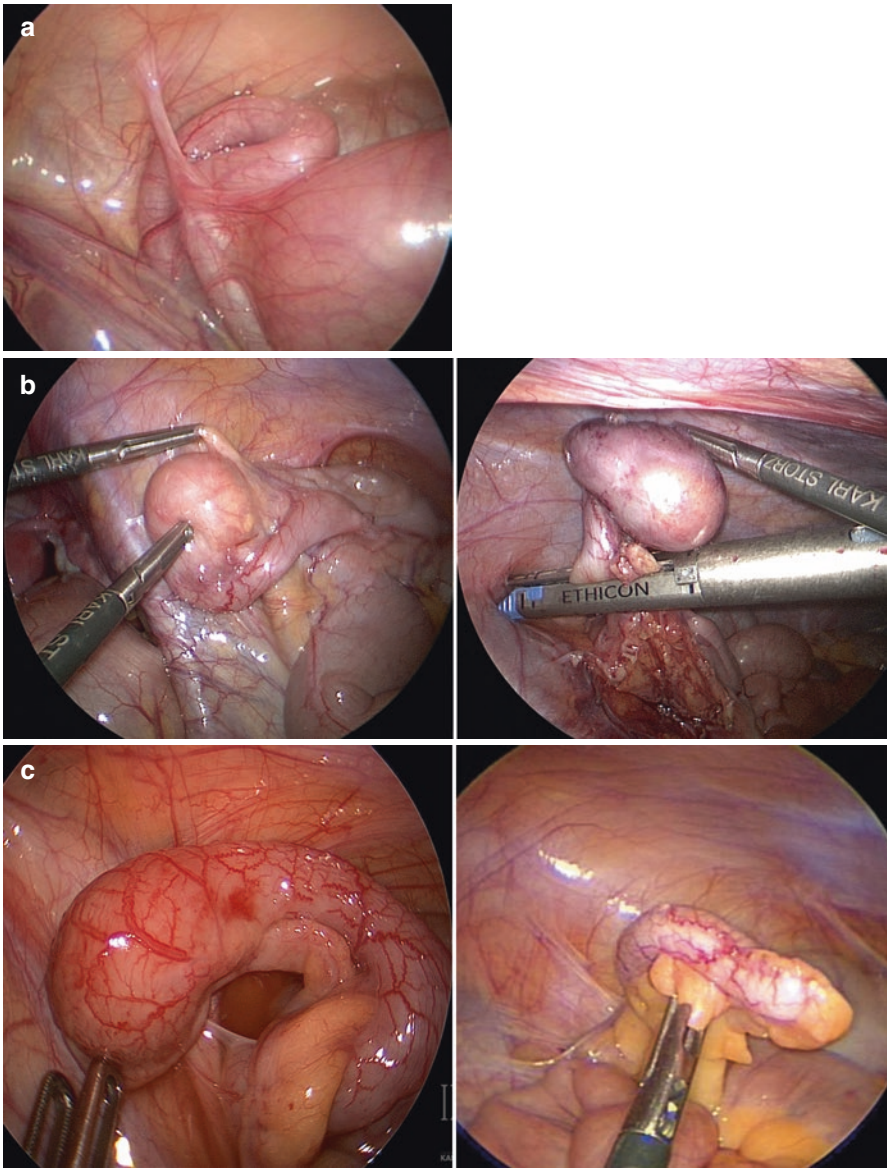

Fig. 43.39 (**a**) Appendix adhesions in a patient with endometriosis. (**b**) Appendix with a large tip, suspected of endometriosis. (**c**) Appendectomy in a patient with chronic pelvic pain, suspected of having endometriosis. (**d**) Appendix with a very large tip and omental adhesions

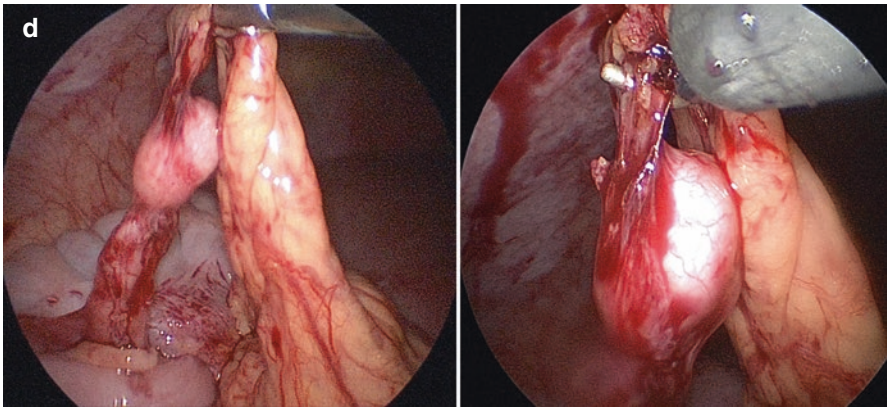

Fig. 43.39 (continued)

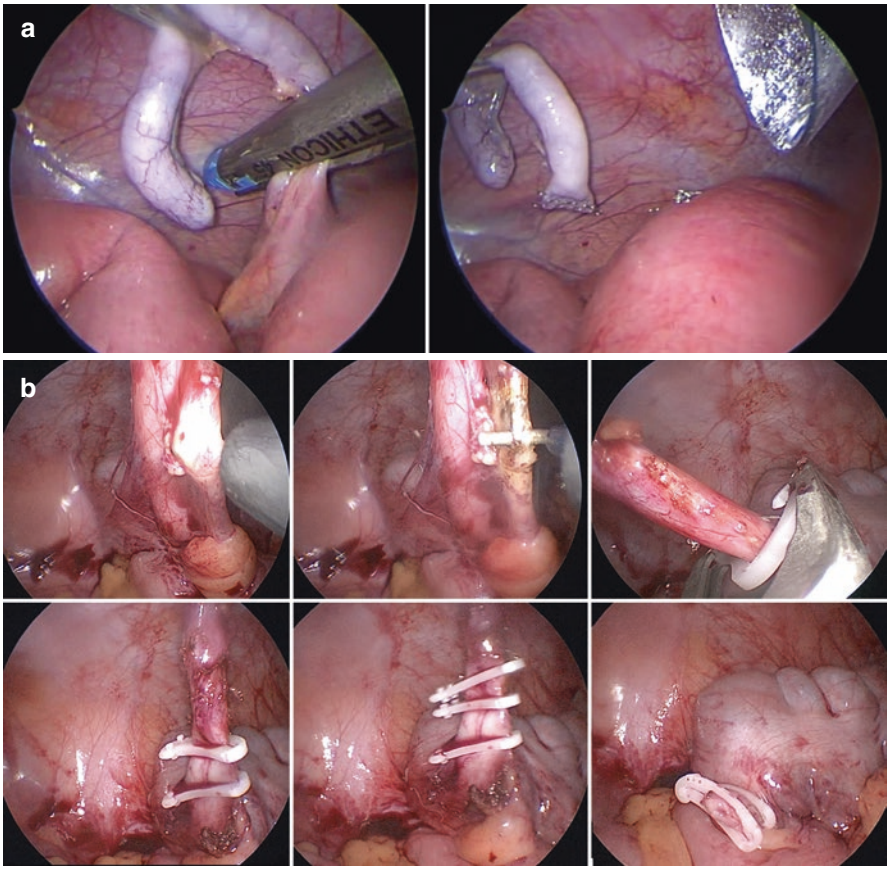

Fig. 43.40 (**a**) Appendectomy with endostapler. (**b**) Appendectomy with hook electrocautery and endoclips. (**c**) Appendectomy with Vicryl endoloops ™

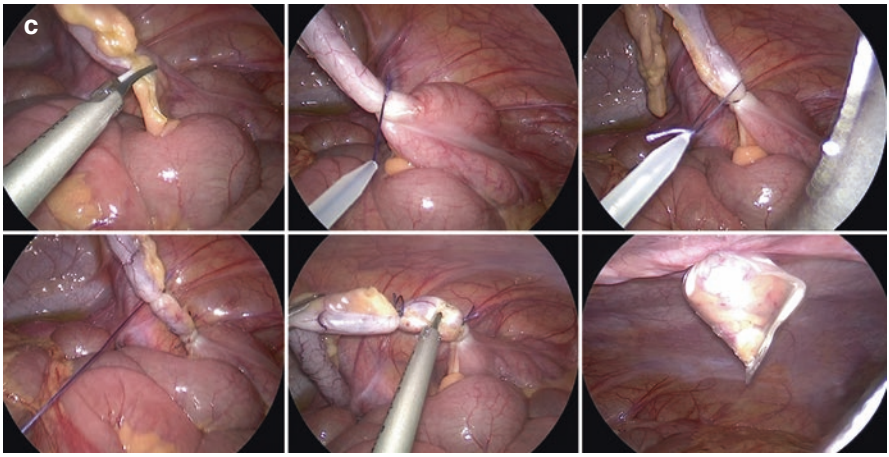

Fig. 43.40 (continued)

Conclusion

The surgical management of endometriosis in adolescents requires a multidisciplinary team approach. Informed consent should include a clear explanation of the endoscopic procedure planned, its benefits, risks, and possible complications, including the possibility of conversion to an open procedure. Preoperative preparation and patient positioning are essential. It is important to prevent and avoid entry complications, as it is stressful to start a potentially difficult operation with an access complication, which can be minor or very severe. There are several laparoscopic entry techniques; the best and safest technique depends on the surgeon's expertise. The anesthesiologist plays an important role, as many patients suffer from chronic pelvic pain and receive long-term analgesic and opioid treatment. Effective management of postoperative pain is essential for an effective recovery. Most cases of chronic pelvic pain are managed by gynecologists. The non-gynecological surgeon operating on adolescent patients with chronic pelvic pain needs to be able to recognize endometriosis and should request help from a gynecology colleague. The diagnosis of endometriosis must be confirmed by biopsy and histological examination. The presence of adhesions can complicate any laparoscopic procedure. They are the most common cause of intestinal obstruction, and they can increase operative time and morbidity. Their role as a cause of chronic pain is debated. Incidental findings during laparoscopy, such as Meckel's diverticulum, can cause complications and may require the help of a general or pediatric surgeon. Because the appendix plays an important role in the etiology of acute and chronic pain, it has been recommended that appendectomy should be performed during laparoscopy for chronic pelvic pain and in cases of endometriosis. The appendix itself may be involved in a significant number of patients with pelvic endometriosis. Appendectomy, however, remains controversial.

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Part XIII
Today's Activism: Increasing Awareness Among Physicians and Patients

Chapter 44
Approach to Diagnosis of Adolescent Endometriosis for the Primary Care Pediatrician

Joy A. Maxey

This chapter will explore the diagnostic approach to endometriosis in adolescents for the primary care pediatrician. The first part will discuss "typical" presentations, i.e., adolescents presenting with pelvic and/or menstrual pain. The second part will cover "atypical" presentations, e.g., adolescents presenting with gastrointestinal, musculoskeletal, neurological, or other systemic complaints. This approach is based on my 30 years of experience in general pediatric private practice in an urban setting. My patients have taught me much over the years and have helped me refine my approach to diagnosis and management.

Part I. "Typical" Presentations: Approach to the Adolescent Patient with Complaints of Pelvic and/or Menstrual Pain

As with any complaint of pain anywhere in the body, the first and one of the most important steps is to utilize a basic skill we were all taught in medical school: take a detailed history regarding the pain. When was the pain first noticed? Where exactly is the pain located? How severe is the pain on a 5- or 10-point scale? Does the severity fluctuate? Does it seem to be associated with time of day? Activities? What makes the pain better? What makes it worse? Does the pain migrate? If so, where? Is it constant, intermittent? If it's intermittent, does it last for a few hours, a few days, how long? What is the quality of the pain? Is it sharp, dull, achy, throbbing, crampy, etc.? Does it interfere with sleep? Does it interfere with daily activities? Does it interfere with leisure activities? Is it associated with menses, or does it occur at other points during the cycle? Are there other concurrent symptoms, e.g., nausea, diarrhea, headache, rashes, and joint pain? Are there any treatments that have been

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tried in the past? Did the treatments help? If so, was it a slight improvement? A great improvement?

After taking the detailed pain history, take a family history. Are there any relatives with a history of similar symptoms? If so, how many and what relation to the patient? How old were they when they had the symptoms? What was the family member's diagnosis? What treatments helped them?

Complete the Review of Systems

It serves as a good cross-check to the question regarding concurrent symptoms, asked during the history of present illness. Pay particular attention to the menstrual history as well as other related systems.

Physical Exam

In addition to a detailed abdominal and pelvic exam, make sure to examine other systems appropriate to any non-pelvic concurrent symptoms such as headache, rashes, or arthralgia. It may not be possible to do a pelvic exam on every patient, especially young adolescent patients. In the cases where an exam cannot be performed, a cotton-tipped swab inserted into the vagina can give information as to the patency of the vagina and can provide indirect information regarding obstructive or partially obstructive anomalies such as a transverse vaginal septum, imperforate hymen, vaginal agenesis, or an obstructed hemivagina [1].

Lab Evaluation

Laboratory tests to consider include complete blood count and erythrocyte sedimentation rate, which may suggest the presence of an acute or chronic inflammatory process; urinalysis and urine culture to identify pain originating in the urinary tract (e.g., cystitis, stone); pregnancy test; and tests for sexually transmitted infections (gonorrhea, chlamydia), which may be indicated in selected group of patients [2]. Nezhat Endometriosis Advisor, a free download app from Apple and Google, with a list of questions for the patients to asses their risk of Endometriosis.

Imaging Studies

Especially if the pelvic exam was limited or unable to be obtained, abdominal and/or pelvic ultrasound may be useful to identify or exclude the common structural causes of pelvic pain in adolescents, such as ovarian cysts, ovarian torsion or

hemorrhage, tumors, genital tract anomalies, and appendicitis [3]. At times MRI may be indicated.

Assessment

After evaluating the patient and finding no apparent causes for the pelvic and/or menstrual pain, the common working diagnosis for most adolescents is primary dysmenorrhea. It is well documented in the literature that the approach to the patient with this diagnosis is a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or a trial of oral contraceptives (OCs) [1]. If after 3 months of combination therapy, the patient is still experiencing pain, albeit improved, a consideration of a diagnosis of secondary dysmenorrhea should be entertained.

Part II. "Atypical" Presentations: Approach to the Adolescent Patient with Other Presenting Complaints

In this section, we will discuss adolescent females presenting with non-pelvic/menstrual pain complaints, i.e., headaches, nausea, stomachaches, arthralgia, rashes, etc. The purpose is to present the thought of considering secondary dysmenorrhea and possible endometriosis when the patient's seemingly unrelated symptoms are not resolved with the usual approach to diagnosis and treatment of the presenting symptom(s).

The following vignettes are presented to illustrate the concept:

Patient #1 is an 11-year-old Asian decent female whose primary complaint was fatigue. The initial history and physical exam was consistent with diagnosis of allergic rhinitis, and she was placed on appropriate therapy. Within a few weeks, she presented with a complaint of headache, was diagnosed with sinusitis, and was placed on a round of antibiotics. The allergy symptoms continued to worsen despite being compliant with the prescribed allergy regime, and the sinus infections were becoming more frequent. Also the fatigue persisted, so the patient was referred to an allergist for further evaluation and treatment. In addition to allergic rhinitis, the workup with the allergist also revealed that the patient had signs of gastroesophageal reflux disease. The patient was started on Tagamet in appropriate doses and immunotherapy. Allergy symptoms improved, the sinus infections stopped, but the patient continued to have fatigue. Further lab evaluation showed that the patient had acquired an acute Epstein-Barr viral infection. The patient's fatigue eventually resolved.

Approximately 6 months later, she presented again with fatigue and headache and was diagnosed with influenza. These symptoms resolved within the timeframe expected for the diagnosis. Six months after the influenza diagnosis, she presented with complaints of headache and increasing fatigue and was diagnosed with a viral

illness. The headaches continued to increase over the next 4 weeks until the pain was severe and unrelenting. CT scan and MRI showed no abnormalities and neurological evaluation determined she was having migraine headaches. She was started on a migraine treatment protocol with minimal success. By this time in her course of illness, the patient had to be withdrawn from school and was being homeschooled. Because it seemed as though her headaches had some relationship with her menstrual cycle, the patient saw an OB-GYN, who felt there was not a hormonal contribution to the headaches, primarily because the cycles were normal. The patient was also evaluated by a pain specialist, without much relief. Because the patient's headache pain was so debilitating, her parents sought consultation with a functional medicine specialist, who after taking a very detailed history referred the patient to a reproductive endocrinologist. The patient was placed on metformin and a gluten, dairy, and soy-free diet with complete resolution of the migraines. She is now back in school and doing well. Time from initial presenting complaint to diagnosis – 4½ years.

Take-home points:

- Even with a normal cycle, endometriosis and/or polycystic ovarian syndrome (PCOS) can be a contributor to migraine headache [4].
- It is always worth revisiting and getting a more detailed history regarding the patient's menses and other symptoms which occur during the cycle.

Patient #2 is a 14-year-old Caucasian female who presented with a complaint of digestive issues, constipation, and abdominal pain. Initial evaluation resulted in a diagnosis of gastroesophageal reflux disease. The patient was placed on appropriate step therapy regimen and dietary modifications were made. Symptoms improved greatly but did not resolve completely. The patient presented approximately 1 year later with a complaint of arthralgia. There were multiple joints involved and the pain was migratory. Laboratory evaluation did not reveal any abnormalities. The pain would improve with nonsteroidal anti-inflammatory agents but did not completely resolve. Nine months after the diagnosis of arthralgia, the patient presented with a marked exacerbation of her GI symptoms, including severe abdominal pain, alternating constipation, and diarrhea and hematochezia. A referral to a gastroenterologist was made, and after evaluation, the patient was diagnosed with Crohn's disease. Within 3 months of her Crohn's diagnosis, the patient had an exacerbation of her migratory arthralgia. Consultation with a rheumatologist resulted in a diagnosis of rheumatoid arthritis (RA). The patient was also having severe dysmenorrhea and metrorrhagia. She sought consultation with a gynecologist, who placed her on oral contraceptive pills. When asked about her menses during a routine well child check, she disclosed her consultation with the GYN and stated that the OCs had improved but did not eliminate her symptoms. Consideration was given as to whether she had secondary dysmenorrhea. She was referred to a reproductive endocrinologist for further evaluation. Her final diagnosis was endometriosis. Unsurprisingly, her Crohn's and RA symptoms improved with treatment of her endometriosis. Time from initial presenting complaint to diagnosis – 8½ years.

Take-home points:

- There is an increased association with autoimmune disorders such as Crohn's and RA with endometriosis [5, 6].
- Remember to ask specific questions regarding the menses and accompanying symptoms during routine adolescent well child checks.

Patient #3 is a 15-year-old Caucasian female who presented with a complaint of recurring rash and severe acne on her back. A diagnosis of atopic dermatitis and acne vulgaris was made. Usual therapy was initiated. After two therapeutic changes in treatment regimens, both the atopic dermatitis and acne were slightly improved but certainly not resolved. A referral was made to dermatology. Their assessment was the same and new therapies were initiated. The atopic dermatitis was substantially improved such that the patient went months between flare-ups as opposed to 2 or 3 weeks. The acne was not much improved, so Accutane was started. During her routine well child check, when asked about her acne, the patient and her mother expressed frustration that the acne still was not substantially better even on Accutane and were concerned about the side effects and risks of the medicine. Upon further inquiry regarding her menses, the patient disclosed she had very painful periods, helped somewhat by NSAIDs, and that she "just sucked it up" and went on about her daily activities during this time. She had been on a course of OCs in an effort to help her acne, before she started the Accutane. She stated that the pills had "really not helped" her painful periods. A diagnosis of secondary dysmenorrhea was entertained. She was referred to a reproductive endocrinologist. Her final diagnosis was PCOS and endometriosis. She was treated appropriately and her acne and atopic dermatitis completely resolved. Time from initial presenting complaint to diagnosis – 5 years.

Take-home points:

- There is an increased association of endometriosis in women with allergies and asthma [7].
- Many adolescents accept pain and interference with daily activities as "normal." It is not. An approach to consider is to ask "Do you have *any* pain associated with your period?" It's a yes or no question. If yes, then quantify; is it mild, moderate, severe, or whatever pain scale is used in your practice. If no, reaffirm that the patient really means no and doesn't mean something along the lines of "nothing unusual" or "nothing that I can't deal with."

Patient #4 is a 16-year-old African American female. She presented with complaints of feeling tired and nervousness. Patient was an A student in school. No family stressors or recent changes in friends were reported. Family history was positive for "thyroid disease" in the maternal grandmother. The patient was noted to have a borderline sized thyroid gland with no other abnormal findings. Laboratory evaluation was consistent with a diagnosis of Graves' disease. The patient was placed on appropriate medication with good results. She had appropriate follow-up visits. Approximately 1 year after diagnosis, the patient presented with a complaint

of painful periods. Her thyroid labs were normal. She was started on a trial of NSAIDs and OCs. Upon reevaluation at 3 months, her pain was better but not completely resolved. She was able to go about her usual activities during her menses since starting on the NSAIDs and OCs. The decision was made to continue on the current therapy and to call should the pain become worse. Approximately 11 months later, during her well child check, she was asked about her menstrual periods. She reported that the pain had become gradually worse, but "it wasn't bad enough to come back in" for an appointment. She was changed to a different OC. She was reevaluated 3 months later, and it was found that her pain had not improved compared to the first OC. Consideration was given to the diagnosis of secondary dysmenorrhea. She was referred to a reproductive endocrinologist. Further evaluation revealed a diagnosis of endometriosis. An appropriate management plan was implemented with resolution of her symptoms. Time from initial presenting complaint to diagnosis – 3½ years.

Take-home points:

- There is an increased association of endometriosis in patients with Graves' disease [8].
- If not already in place in your practice, consider implementing a system to do a phone follow-up with patients who have risk factors that place them at increased risk for endometriosis.

Conclusion

Endometriosis is an inflammatory disorder which may be associated with autoimmune disorders. It can be in coexistence with other disease and have variable manifestations. Nezhat et al. found patients (n = 25) with a mean age of 17.2 had experienced symptoms for an average of 22.8 months and seen a median number of 3 physicians before receiving an accurate diagnosis [9]. Adolescents with onset of these symptoms associated with menarche must be evaluated for endometriosis.

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Chapter 45
Individual Actions

Erica Mark

My journey into medicine was gradual. I knew I wanted to help people and that I possessed a genuine curiosity and aptitude for science. However, unlike many of my peers, I did not have that one "aha" moment that redirected the trajectory of my life and landed me firmly at the footsteps of a medical career. It was through meeting physicians such as the Drs. Nezhat and the other passionate, selfless physicians, medical professionals, and activists affiliated with Worldwide EndoMarch that the light at the end of the tunnel became focused and I could clearly see my dream—to help people during their most vulnerable times.

In today's world, the importance of patient advocacy has never been more apparent. We have more resources, more knowledge, and more effective ways of communicating with each other than ever before. Yet, even with all the advantages of the modern era, there is still a long way to go—especially in the field of female reproductive healthcare. One in ten women are statistically likely to have endometriosis, and this is a conservative estimation in the minds of leading experts in the field [1]. Despite the prevalence of endometriosis, it takes an average of 6 to 10 years for a woman to obtain a diagnosis [2, 3]. Nezhat et al. found that patients (n = 25) with a mean age of 17.2 had experienced symptoms for an average of 22.8 months and seen a median number of 3 physicians before receiving an accurate diagnosis [4]. And even if a diagnosis is obtained, treatment options are limited and typically involve the surgical removal of affected organs—commonly reproductive organs, induction of premature menopause, pregnancy, birth control, or the age-old "grin and bear it" prescription [5–7].

Endometriosis is not a new phenomenon; for centuries, women have chronicled their experiences dealing with symptoms that we can safely assume to be indicative of endometriosis [5]. However, our understanding of endometriosis, and certainly the female reproductive system in general, has increased exponentially in the

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ensuing centuries. For example, the ancient Greek practice of "succussion," during which the female patient is shaken fervently while hanging upside down from a ladder, has passed and given way to more humane and scientific treatments [5] (Fig. 45.1).

Nevertheless, given the disappointing statistics on the ability to successfully diagnose endometriosis in a timely manner, many concerned physicians and patient advocates have raised the question—how far have we really come?

The fight to increase awareness about endometriosis has been hindered by several major obstacles. First, within society there exists an idea that painful periods are normal. For example, I personally have assisted my friend in retrieving a heating pad during a particularly torturous round of period cramps without giving it a second thought. Midol, tea, and bed rest—that's the cure, right ladies? I never would have suspected that something much more insidious could be the culprit of what I considered just another female burden—and I am not alone. From the onset, pubescent girls are taught by mothers, sisters, aunts, friends, teachers, and even doctors that painful periods are a normal and an innocuous ordeal endured by the female sex. Those within the 10% of women who have endometriosis and are unfortunate enough to experience significantly painful periods are considered either unlucky or weak for being unable to cope with an experience all women seemingly share. In order to achieve complete awareness and lower the diagnosis time, such notions need to change; when your daughter, sister, niece, friend, student, or patient

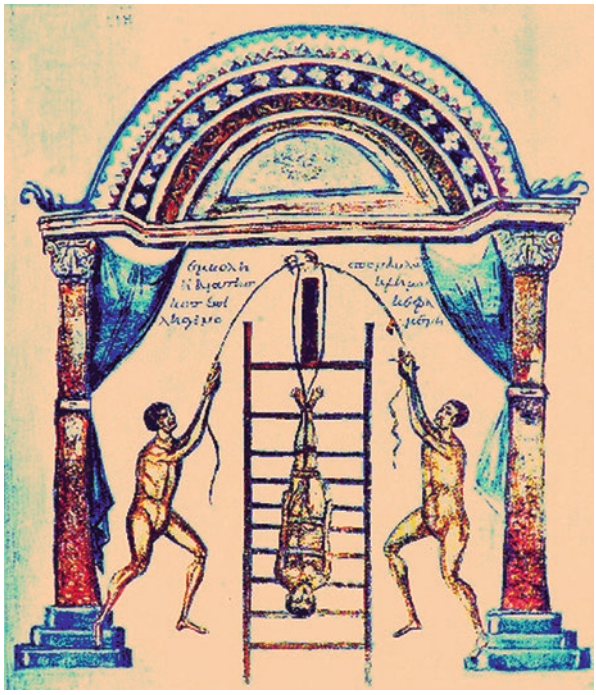

Fig. 45.1 Uterine suffocation, vaginal prolapse, and other gynecologic conditions were sometimes treated with succussion, the ancient Greek practice in which patients are bound to a ladder, turned upside down, and shaken vigorously, with the idea being that the uterus would be shaken back into its proper position. (Reproduced courtesy of BioMed Central Ltd and SpringerImages. Scoliosis 2009;4:6. Image from the illustrated comments of Apollonius of Kitium on the Hippocratic treatise On Articulations. Bibliotheca Medica Laurenziana, Florence. Nezhat. Endometriosis in history. Fertil Steril 2012)

confides in you about her painful periods, ask more questions. Ask if she has talked to her OB/GYN about her symptoms and begin a discussion about endometriosis.

Secondly, the stigma surrounding issues regarding female reproductive healthcare must be shattered. In order to have a productive dialogue and increase awareness about endometriosis, as well as other gynecological conditions, women cannot feel embarrassed or ashamed. Conversely, spokespeople with large audiences must lobby for increased research funding. And those in the medical field must work in tandem to eliminate any discomfort promoting the topic, as endometriosis is an issue affecting, and of great concern to, a large portion of the population. An advocate from the Jamaica branch of Worldwide EndoMarch shared with me that her greatest struggle with organizing EndoMarch events is publicity; in one instance, a radio host refused to let her publicize her events because he said that endometriosis was not a "sexy" disease. The taboo nature of infertility, periods, and various diseases of the female sex organs have decreased the medical standard of care for female reproductive health issues by quieting the dialogue, hampering awareness, and reducing funding and resources badly needed to solve the problem. We, as patient advocates, are in a unique position to shatter the stigma simply by talking, sharing, and humanizing a condition that affects one in ten women.

Thirdly, endometriosis has the misfortune of being an invisible disease. Patients routinely face disbelief and doubt regarding the severity of their symptoms. Many women describe the people in their lives as viewing them as lazy, weak, histrionic, or even mentally ill. In the transgender community, especially, symptoms regarding endometriosis are less frequently matched with a diagnosis due to poor education about the nature of the condition [8, 9]. It is shocking to some that endometriosis can be discovered on extragenital organs even after the uterus is removed. In fact, endometriosis has been found on nearly all the organs in the body [6]. The emotional reaction from patients after hearing the doctors say "The pain is not in your head. It is real. I see it and I believe you" is at both times moving and disconcerting. This is not to say that society is cruel or apathetic. Many people are unaware. Sick people normally look, well, sick! Contrary to the image of the pale, withering invalid that is conjured when the imagination is tasked with putting a face to chronic illness, endometriosis patients are fighting an internal battle sometimes unperceivable to the outward world. To be sure, there are positives that come with the inconspicuousness of the disease: discrimination, pity, and the confluence of one's identity with the disease are challenges that those with more visible conditions might face. But, on the other hand, it also means that society can be less understanding, more skeptical, and less willing to lend a helping hand. In order to meet this challenge, patient advocates must shine a light on the invisible disease through education. The public and training physicians need to be better educated on the condition, its etiology, and treatment protocols. There must be recognition that this condition can be debilitating and improved education in order to be appropriately sympathetic to those persevering every day with endometriosis.

In a more clinical perspective, the broad presentation of endometriosis can result in confusion when comparing it with diseases that have similar symptoms, like irritable bowel syndrome. Endometriosis can present with a multitude of symptoms

such as dysmenorrhea; pain with urination, defecation, or sex; infertility; and abnormally heavy or light periods [6, 7]. The list is long. Adding to this challenge, there is no noninvasive test to confirm a diagnosis of endometriosis—it is typically diagnosed via exclusion or invasive means [6]. Leading experts in the field who have spent their medical careers dedicated to endometriosis treatment can render a fairly accurate prediction regarding whether endometriosis is present—it is, however, a prediction. In order to be certain, the patient must undergo laparoscopy.

Brilliant researchers and physicians are getting closer every day to finding a noninvasive diagnostic tool to identify endometriosis. In the meantime, it is fortunate there are inquisitive and caring physicians willing to—as a particularly concise patient put it—"just dig." Better educating future physicians about the intricacies of endometriosis will inspire them to look further into a patient's history while conducting patient intake and understand that patients are not simply a compilation of symptoms. By asking questions and listening to patients talk about what symptoms they are experiencing, physicians can obtain a deeper understanding of patient physiology and create more effective treatments. Prospective physicians have the opportunity to follow in the footsteps of these brilliant medical professionals and take a broader view of medicine as a means to treat the whole person.

After interning with Professor Camran Nezhat one summer while in university at the University of California, Los Angeles, I became involved with Worldwide EndoMarch. I was touched by the testimonials of patients living with endometriosis. Countless women came to Professor Nezhat with vignettes of a similar story: they had been told that painful periods were normal and symptoms such as infertility or abdominal pain existed only in their heads. In extreme cases, some women mentioned being referred to psychological services rather than reproductive specialists in order to deal with the pain.

Unfortunately, this pattern exists due to a lack of awareness and a deficit in funding of research regarding female reproductive health issues. Prospective physicians are in the unique position to learn and expand their roles as patient advocates. It is important for those on the front line of healthcare to fight for awareness about both the medical and nonmedical impediments to living a healthy life. In the United States, especially, where we are encountering more chronic diseases, the responsibility of the physician to be a patient advocate has grown. The role of the medical profession should be to equip all persons with appropriate health education, encourage the practice of self-care, and provide appropriate referrals to specialists in this field. Although it is a partnership between the medical professional and the patient, physicians have a responsibility to advocate for the health of the members of their community.

Today, I see TV ads featuring endometriosis awareness campaigns and pharmaceutical companies scrambling to synthesize new drugs to capitalize upon the lucrative market of endometriosis patients seeking noninvasive forms of relief. It may be easy to take for granted that the bolstered representation of endometriosis in the media is recent and, in my opinion, has largely coincided with corollary awareness campaigns aimed at elevating female rights such as the #MeToo movement. Yet,

female reproductive healthcare *is* a right and it makes sense that as the status of women in society is elevated, so too is their standard of health.

In this complex web of influence, there are many ways to become an advocate. One can be an advocate from the comfort of his or her own home simply by being authentic and sharing a personal journey via social media. Or one can get organized and start a grassroots movement within his or her community by starting a support or outreach group, raising funds for research, reaching out to political representatives, or volunteering with physicians or organizations in a field of interest. My journey began when I did the latter. By getting involved with Worldwide EndoMarch, I have been able to connect with experts, patients, and powerful patient advocates all working together to reach a common goal: increase the medical standard of care and societal awareness for people suffering from endometriosis. I am grateful to say that my experiences have made me more optimistic about our future than ever before. Oftentimes I am asked why I chose to get involved with endometriosis advocacy and Worldwide EndoMarch. And while there are several reasons ranging from personal connections to the disease and having a general interest in the disease, the biggest factor fueling my passion for endometriosis advocacy is unequivocally the patient population. Those affected by endometriosis are truly the most resilient and hopeful people I have ever met and working with them has made me a better person and hopefully one day a better physician.

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