Cost Estimates Associated with Diagnosis and Treatment of Endometriosis

28

Brintha Sivajohan, Tinya Lin, and Mohamed A. Bedaiwy

Contents

B. Sivajohan
Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

T. Lin
Department of Obstetrics and Gynecology, The University of British Columbia, Vancouver, BC, Canada

M. A. Bedaiwy (✉)
Department of Obstetrics and Gynaecology, BC Women's Hospital and Health Center, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada
e-mail: mohamed.bedaiwy@cw.bc.ca

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28.1 Introduction

28.1.1 What Is Endometriosis?

Endometriosis is a chronic condition characterized by the growth of endometrial-like tissue outside the uterus with varying degrees of severity and non-specific symptoms [1]. Endometriosis commonly presents in pelvic locations such as the ovaries as endometriomas, peritoneum, bowel, and bladder amongst other less common locations such as the lungs, liver, and inguinal region with a range of symptomatology affecting multiple organ systems [2, 3]. The broad spectrum of this disease can be classified as three predominant phenotypes (Fig. 28.1): superficial

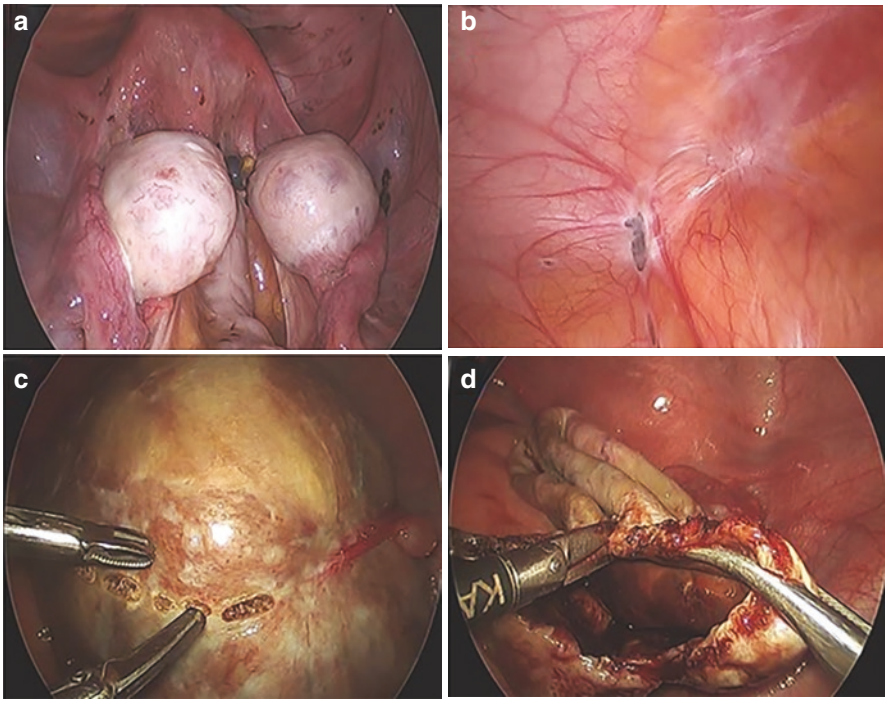

Fig. 28.1 Three different phenotypes of endometriosis. From left to right, starting from the top, the three different phenotypes of endometriosis are shown: (**a**) deeply infiltrating endometriosis (DIE), (**b**) superficial peritoneal endometriosis, and (**c**) ovarian endometriomas with (**d**) excision of the ovarian endometrioma cyst. Figures courtesy of Dr. Mohamed Bedaiwy

peritoneal, endometriomas, or deeply infiltrating endometriosis (DIE) [5]. DIE occurs when the endometrial-like tissue penetrates the peritoneal space either 5 mm or more [2]. Due to its clinical heterogeneity, symptoms range from dysmenorrhoea and dyspareunia to chronic pelvic pain and infertility [1]. Reproductive-age women between the ages of 35 and 44 have been shown to be at highest risk for this chronic condition [6]; however, cases have been documented in pre-menarcheal girls and post-menopausal women [3]. Despite significant strides in the field, the pathogenesis of this disease is still not clear. There is a growing body of literature pointing to the importance of immunological, inflammatory, genetic, and environmental factors and their interactions in the aetiology of endometriosis [7, 8].

28.1.2 What Is the Prevalence of Endometriosis?

It has been estimated that close to 176 million women globally are impacted by this disorder [9, 10], encompassing about 10% of reproductive-age women [10, 11]. Since definitive diagnosis is only established through surgical histopathology, the true prevalence is difficult to elucidate and likely significantly underreported [10]. Louis et al. [12] estimated that approximately 11% of American women may have endometriosis during their reproductive years despite being asymptomatic and presenting with no complaints.

The majority of prevalence studies are in women who are symptomatic. One US study found endometriosis in 23% of women undergoing diagnostic laparoscopy for dysmenorrhoea and infertility [13]. The prevalence of endometriosis amongst women exhibiting infertility and chronic pelvic pain has been estimated to be between 30% and 50% [14]. In infertile women with regular ovulatory cycles and partners with healthy sperm, the prevalence rate increases up to 50% [14]. Studies in adolescents with severe dysmenorrhoea demonstrate that about 50–70% of individuals receive a diagnosis of endometriosis [12]; however, there are very few studies that look specifically at adolescent populations. About 24–40% of women presenting with chronic pelvic pain are diagnosed with endometriosis making this condition the most common cause of chronic pelvic pain [15, 16]. In brief, between 35% and 50% of symptomatic women are impacted by endometriosis [17].

28.1.3 What Are the Signs and Symptoms of Endometriosis?

The documented signs and symptoms of endometriosis are non-specific and vary in degree of severity amongst patients. Table 28.1 illustrates some of the common signs and symptoms that are reported in patients with endometriosis. Due to its clinical heterogeneity, patients with endometriosis can present with a vast array of symptoms including chronic pelvic pain, dysmenorrhoea, and deep dyspareunia with variable intensity and combination of these symptoms. Patients can also present with bowel and urinary symptoms such as dyschezia, dysuria, haematuria, and abdominal pain [3] which can correlate with the anatomical location of endometriosis implants.

Table 28.1 Signs and symptoms of endometriosis

Signs and symptoms
Dysmenorrhoea
Heavy menstrual bleeding
Cyclical or non-cyclical abdominal pain
Chronic fatigue
Nausea, vomiting
Pelvic pain
Dyspareunia
Bowel symptoms:
Constipation
Diarrhoea
Dyschezia
Urinary symptoms:
Dysuria
Haematuria
Subfertility/Infertility

Reference: [3]

Some patients remain asymptomatic until they present with unexplained infertility. The vast majority of these symptoms are also present in patients with pelvic inflammatory disease, irritable bowel syndrome, adenomyosis, and overlap with many other chronic pain disorders such as pelvic floor dysfunction [18]. Non-specific symptoms in combination with a lack of healthcare provider awareness can lead to the misdiagnosis and under diagnosis of endometriosis.

28.1.4 What Are the Impacts of Endometriosis?

Due to the chronic and debilitating nature of this disease, there are various impacts on multiple domains across a patient's life course. The chronic symptoms of endometriosis, such as pelvic pain, dysmenorrhoea, and dyspareunia, increase healthcare resource utilization as well as negatively impact patients' health-related quality of life and emotional well-being. The next section will breakdown the various impacts of endometriosis on patients and healthcare systems.

28.1.4.1 Impacts on Health-Related Quality of Life

Studies demonstrate that endometriosis contributes to significant impairments of psychosocial functioning and health-related quality of life (HRQoL) [19]. In comparison to asymptomatic controls with no diagnosis of endometriosis, physical HRQoL was significantly impaired in women with endometriosis [10], specifically on physical functioning and body pain scores. Physical HRQoL was more pronounced than mental HRQoL. Scores on the Short Form Health Survey Questionnaire in patients with endometriosis were similar to patients with cancer [10, 20]. Another study [21] used scores on the Endometriosis Health Profile (EHP-5) to demonstrate that 43% of patients with endometriosis reported that pain interfered with work substantially and 41% reported physical impairments (i.e. difficulties walking). Patients who experienced delays in receiving a diagnosis had even greater reduced

HRQoL, and this reduction remained significant after adjusting for the number of symptoms [10].

28.1.4.2 Impacts on Fertility

Approximately 30–50% of women diagnosed with endometriosis experience fertility issues, and about 20–50% of women presenting with concerns of infertility are diagnosed with endometriosis [22]. Senapati et al. [23] suggested that damage to the ovarian cortex can occur from endometriosis, or from surgical treatments (i.e. removal of endometriomas). This results in the need for increased gonadotrophin stimulation and fewer retrieved oocytes with stimulation for in vitro fertilization (IVF) [23]. The impacts of endometriosis on infertility often result in the need for more advanced reproductive planning, more visits to reproductive specialists, more invasive management options, higher stress on romantic relationships, and increased financial costs for patients.

28.1.4.3 Impacts on Psychosocial Functioning

Psychosocial functioning is significantly impacted by endometriosis, with studies demonstrating effects on general psychological well-being, sexual dysfunction, and relationships with partners. The most common symptoms of endometriosis include chronic pelvic pain and infertility which negatively impact psychological well-being in many patients. The stigma and social implications of endometriosis in combination with dealing with emotionally taxing symptoms are strong predictors of psychological distress in patients [24, 25]. Chronic pain in endometriosis associated with reproductive anatomy can carry a higher psychosocial cost attached to it due to the far-reaching impacts on infertility/subfertility, sexual discomfort, and interpersonal relationships as opposed to other chronic pain problems [26]. Endometriosis often leads to dyspareunia and sexual dysfunction which negatively impacts relationship adjustment and overall quality of life [26]. In addition, the chronic nature of this disease often demands the need for long-term treatment and is accompanied by a high risk of recurrence and progressive symptomatology which can exacerbate psychosocial functioning in patients.

Focus group studies have shown that aspects of psychosocial functioning such as everyday activities, life opportunities, and personal finances are extensively affected by having endometriosis [27, 28]. Future studies should explore how social support mitigates these real and perceived negative impacts.

28.1.4.4 Impacts on Employment and Work Productivity

Nnoaham et al. [10] found that women with endometriosis missed approximately 11 hours of employment per week. This loss was mainly due to presenteeism (reduced productivity while at work) rather than absenteeism (absence from work). The researchers noticed that patients' working capacity and capabilities were restricted due to their symptoms, and consequently, many opted to resign, switch roles, or use more allocated sick days resulting in loss of work productivity. These results align with prior findings demonstrating a strong correlation between pain severity and interference with work productivity [18]. Another study reported a significant association between adolescents experiencing severe dysmenorrhoea and

absenteeism from school and work with 12% of individuals reporting monthly absences from school and work due to dysmenorrhoea [29]. Soliman et al. [30] reported an average weekly loss of 5.3 hours due to employment presenteeism and 1.1 hours lost due to employment absenteeism in women with endometriosis.

28.1.5 Why Are Costs of Endometriosis Important?

Endometriosis poses large direct and indirect costs to patients and society. In the USA, the annual economic burden of endometriosis was estimated to be $22 billion in 2002 [31] and climbed to $69.4 billion in 2009 [32]. Soliman et al. [33] conducted a systematic review of studies published from 2000 to 2013 and estimated direct costs to be close to $12,118 per patient annually while indirect costs were around $15,737 per patient annually. Despite these staggering numbers, they are likely an underestimate of the true costs to society due to the lack of data on direct non-healthcare costs (i.e. transportation for ambulatory visits, time off from work to attend appointments, and childcare costs during appointments) and indirect costs (i.e. reduced work productivity, caregiver costs, and short- and long-term disability).

Endometriosis is a complex, heterogeneous disease process that has significant financial impacts on healthcare systems. Healthcare systems are constantly under pressure to be as cost-efficient as possible in the face of spiralling healthcare costs and limited resources. There is a strong need for continued evaluation of indirect and direct cost estimates and economic evaluations of diagnostic and treatment methods. Given the prevalence of this disease and its far-reaching impacts on both healthcare and societal productivity, estimated costs of endometriosis burden can support appropriate resource allocation and the formation of cost-effective guidelines. This chapter outlines the cost studies that have identified the major contributors to diagnosis and treatment costs in endometriosis. It will also help inform future priorities in research to ensure that healthcare systems remain sustainable in the face of competing demands.

28.2 Costs Associated with the Diagnosis of Endometriosis

28.2.1 How Is Endometriosis Diagnosed?

The diagnosis of endometriosis is complex, with many challenges that result in additional costs to the patient and healthcare system. Endometriosis is traditionally diagnosed via laparoscopic visualization accompanied by the histologic confirmation of ectopic endometrial-like tissue [3]. Some forms of severe endometriosis such as DIE and endometriomas can be detected using imaging such as MRI or ultrasonography, but histological testing of excised lesions is historically recommended as the gold standard test [3]. Diagnostic procedures include laparotomy or laparoscopy, although the latter is more common [34] due to the benefit of reduced complications, length of hospital stay, and recovery times. A cost analysis study shows that laparotomy ($9533) is twice as expensive as laparoscopy ($5014) in

direct healthcare costs [35] and has poorer outcomes. Laparoscopy also provides better visualization of the peritoneal cavity and has proven better for excising benign ovarian endometriomas [36]. As a result, laparoscopy has been favoured over laparotomy for the purposes of diagnosis [34].

Albeit these advantages, a laparoscopic diagnostic procedure still contributes heavily to the economic burden of endometriosis. Other than the direct healthcare costs associated with a surgical procedure, there is risk of post-operative complications such as surgery adhesion formation resulting in further complications that need management [37]. Currently, this gold standard test to diagnose endometriosis is invasive, costly, and poses some risks to the patient.

Other less invasive and inexpensive methods have been recently explored for the diagnosis of endometriosis. Ling [38] demonstrated that a 78–87% accuracy for a clinical diagnosis of endometriosis can be made using a history that documents symptoms of dysmenorrhoea, abnormal uterine bleeding, and dyspareunia and physical findings typical of uterosacral ligament nodularity. Alternatively, the rule-out method using history and physical evaluation to rule out other possible diagnoses and non-response to empirical treatment such as non-steroidal anti-inflammatory drugs (NSAIDs) and combined hormone contraceptives (CHCs) can be used to diagnose endometriosis accurately 80–90% of the time [38].

Despite research into less invasive methods of diagnosis, laparoscopic surgery followed by histology remains the gold standard diagnostic to detect and stage endometriosis. Due to the cost, potential complications, and invasiveness of laparoscopic diagnostics, it is usually recommended for patients where there is an intention to treat surgically concurrently [3].

28.2.2 What Are the Challenges Associated with Diagnosing Endometriosis?

Diagnosis of endometriosis is often missed in primary care due to non-specific symptoms resulting in delayed or missed diagnoses. Symptomatic women often have symptoms similar to those of other gynaecological, gastrointestinal, urinary, and other chronic pain conditions resulting in a long differential list [39]. Table 28.2 illustrates the many diagnoses commonly on a clinician's differential list when presented with a symptomatic patient. Additionally, a lack of consistent clinical guidelines for diagnosing endometriosis, especially in those with comorbidities, contributes to the difficulties in diagnosing this condition [43].

Another challenge in diagnosing endometriosis is the location of endometriotic growth. Most endometrial-like tissue growth are small lesions that tend to occur in pelvic regions and involve the parietal peritoneum and pelvic organs [3] as superficial endometriosis. As shown in Table 28.3, diagnostic methods such as ultrasound and magnetic resonance imaging (MRI) have not shown significant diagnostic power in detecting endometriosis [39], and diagnosis continues to rely on laparoscopic surgery.

An abnormal pelvic examination and clinical history compatible with common symptoms of endometriosis can be indicative of endometriosis; however, many women are also asymptomatic, and symptomatic women can present with a variety

Table 28.2 Differential diagnosis list for endometriosis

	Differential diagnoses
Gynaecologic causes	Primary dysmenorrhoea Adenomyosis Chronic pelvic pain Pelvic inflammatory disease Uterine fibroids Adnexal pathology Endometrial hyperplasia Endometritis Vaginal infections Cervical polyps Cervicitis Endometrial polyps Pelvic vascular congestion Other neoplasms (benign or malignant) Ovarian torsion
Urinary causes	Urinary tract infection Urethral syndrome Interstitial cystitis/bladder pain syndrome
Gastrointestinal causes	Constipation Irritable bowel syndrome
Other causes	Non-specific low back pain Medications (i.e. hypothalamic depressants) Coagulopathies

References: [3, 40–42]

Table 28.3 Specificity and sensitivity of physical exam, U/S, and MRI in the diagnosis of endometriosis

	Type of endometriosis	Sensitivity	Specificity
Physical exam [44]	Ovarian Endometriosis	23–41%	99%
	Pelvic endometriosis (vaginal, uterosacral ligament)	50–74%	78–100%
	Deeply infiltrating endometriosis (rectum, rectosigmoid, rectovaginal, bladder)	18–88%	54–100%
Ultrasound [45]	Pelvic endometriosis	79%	91%
	Ovarian endometriosis	93%	96%
	Deeply infiltrating endometriosis	79%	94%
MRI [45]	Pelvic endometriosis	79%	72%
	Ovarian endometriosis	95%	91%
	Deeply infiltrating endometriosis	94%	77%

of comorbidities resulting in challenges to diagnose. Prior research has shown that an abnormal pelvic examination correlates with a laparoscopic diagnosis of endometriosis about 70–90% of the time [38]. However, diagnosis should not be excluded on the basis of a normal pelvic exam because research has shown that more than 50% of women with a normal exam have been diagnosed with endometriosis after undergoing laparoscopic surgery [46]. A review by Taylor et al. [44] looked at the accuracy of physical exams as a method of diagnosis in patients with surgically confirmed endometriosis. The specificity, positive predictive value, and negative predictive value of a physical exam were in the range of 80 to 100%, especially for patients with a strong pretest probability of disease based on history. The sensitivity

was much lower and more variable given the greater dependence on lesion location compared to other measures of diagnostic accuracy. Interestingly, studies have shown no correlation between depth and extent of lesions and the corresponding clinical symptoms and presenting complaints [3]. Thus, the ASRM has developed a staging system from stage I—mild to stage IV—severe disease that characterizes location, severity, and depth of endometriotic tissue but does not provide information on the severity of clinical symptoms. While clinicians should remain cautious of the validity of a non-surgical diagnosis of endometriosis, patients can still be managed presumptively while awaiting surgical confirmation.

28.2.2.1 Unnecessary Investigations and Lack of Reliable, Low-Cost Diagnostics for Endometriosis

The diagnostic delay in endometriosis is particularly important as it contributes significantly to the costs associated with diagnosis. Surgical diagnostic methods are invasive and costly, with debatable utility if there is no intent to treat the patient concurrently with surgical methods. The Society of Obstetricians and Gynaecologists Canada (SOGC) recommends using a cost-effective method which includes thorough history and physical evaluation along with transvaginal ultrasound as the first-line diagnostic method [47]. International guidelines also recommend empirical treatment using inexpensive and safe options such as CHCs and progestins when there is a high index of clinical suspicion for endometriosis [1, 47, 48], as 62 to 88% of patients will report improvement in symptoms [49]. Moreover, Frishman et al. [50] reported that only one-third of patients undergoing laparoscopy receive a definitive diagnosis of endometriosis. This demonstrates that a significant portion of diagnostic laparoscopies can be avoided in women with a clinical suspicion of endometriosis, with minimal impact on management, translating into a reduction in unnecessary invasive procedures and costs to the healthcare system.

Non-specific symptoms combined with a lack of healthcare provider awareness can often lead to high healthcare utilization and unnecessary investigations. In fact, women reported an average of seven visits to a primary care physician before receiving referrals to the appropriate specialist (i.e. gynaecologist) [10]. Women with endometriosis who present with urinary symptoms such as dysuria may undergo many unneeded cycles of empiric antibiotic therapy for urinary tract infections [3], adding to the economic burden of this disease and potentially contributing to future antibiotic resistance. Patients with gastrointestinal endometriosis are commonly misdiagnosed as having irritable bowel syndrome due to overlapping, non-specific symptoms, and this can lead to longer delays in receiving appropriate care and unnecessary tests [51]. Patients with higher BMIs also suffer diagnostic delays due to the difficulty in detecting abnormal pelvic pathology on physical examination [10]. However, this underscores the need for heightened awareness of endometriosis amongst primary care and faster referrals as opposed to initiating unnecessary investigations that are not cost-effective nor helpful in establishing a diagnosis.

A lack of non-invasive, reliable tests for first-line diagnostic use is a significant barrier to a cost-effective method for the diagnosis of endometriosis. Many clinical applications have been tested for their reliability and diagnostic power in detecting endometriosis. These include blood biomarkers, urinalysis markers, peritoneal fluid

markers, and imaging techniques for the pelvic region. However, no one method has dominated in larger studies, and many have not shown reproducible results [45]. Better guidelines to approach diagnosis and more reliable diagnostic methods would help alleviate unwarranted costs between symptom onset and definitive diagnosis.

28.2.2.2 What Are the Impacts of a Delayed Diagnosis?

Challenges in diagnosing endometriosis often lead to long delays in patients receiving appropriate care and management. Both patient-centred factors such as stigma, embarrassment, lack of awareness regarding normal and abnormal symptoms, lack of symptoms and physician-centred causes such as inconsistent diagnostic guidelines and unnecessary investigations contribute to the long delays in receiving a definitive diagnosis [52]. Delays in diagnosis vary across the globe but demonstrate years of significant diagnostic delay. Women often have to wait between 6 and 12 years to receive a diagnosis [10, 53, 54], and there is considerable variability between countries in the time taken to receive an endometriosis diagnosis (Table 28.4). Untreated endometriosis during this period has been shown to impact quality of life, mental health, negatively interfere with employment and impact reproduction [19], leading to increased indirect costs and higher costs when treating patients. Studies have identified one main cause for this phenomenon as delays in receiving specialist referrals from primary care providers [10]. In the USA, Soliman et al. [57] documented an average delay of 4.4 years and noted that up to 89% of diagnoses were made only by trained specialists in endometriosis. These results may be indicative of a lack of healthcare provider awareness, and the need for improved diagnostic guidelines for generalists who represent the majority of first-line providers around the world.

In a study by Surrey et al. [58], healthcare resource utilization and endometriosis-related healthcare costs were examined in 11,793 patients with endometriosis who had experienced short, intermediate, and long diagnostic delays. All-cause healthcare costs were highest in patients who had a long diagnostic delay (average of $34460), followed by intermediate delay patients ($30,030), and were lowest in patients who experienced short diagnostic delays ($21,489). In an American,

Table 28.4 Diagnostic delay of endometriosis across different countries

Study	Country	Average diagnostic delay
Arruda et al. [55]	Brazil	Median time between onset of initial symptoms and definitive diagnosis is 7 years
Husby et al. [56]	Norway	Average diagnostic delay of 6.7 +/−6.2 years
Ballard et al. [52]	UK	Median diagnostic delay of 8.5 years
Nnoaham et al. [10]	Italy, China, Brazil, USA, UK, Spain, Nigeria, Belgium, Ireland, Argentina	Average diagnostic delay of 6.7 years across all 10 countries with a range of 3.3 years (China) to 10.7 years (Italy)
Prast et al. [53]	Austria	Average diagnostic delay of 10.4 years before receiving a conclusive diagnosis
Soliman et al. [57]	USA	Average diagnostic delay of 4.4 years

Medicaid-insured population, endometriosis patients showed higher all-cause healthcare resource utilization than age-matched controls during the pre-diagnosis period [59]. This was consistent with another study by Fuldeore et al. [60] which reported that patients with endometriosis spent $7028 more in healthcare utilization costs in comparison to matched controls in the 5 years leading up to diagnosis. Patients who had the longer delays had more endometriosis-related symptoms, endometriosis-related emergency visits, and in-patient hospitalizations in their pre-diagnosis period in comparison to those with shorter delays [58, 60]. The mean frequency of in-patient hospitalizations increased as a function of increasing diagnostic delay, further adding to increasing costs.

In a 60-month period prior to receiving a definitive diagnosis, patients who experienced longer diagnostic delays also reported more insurance claims for endometriosis symptoms and endometriosis-related comorbidities [58]. In the 5 years prior to diagnosis, patients with short delays spent $4298 per year on average on all-cause and endometriosis-related healthcare costs and patients with long delays spent $6892 per year—a 130% increase in endometriosis-related costs annually compared to patients with short delays [58]. Fuldeore et al. [60] used a claims database to report annual costs ranging from USD $3730 in the fifth year prior to diagnosis to USD $6649 in the year immediately prior to diagnosis—also demonstrating that costs incurred by patients and healthcare systems increase as the diagnostic delay gets longer.

Ambulatory visits appear to be a major driver of many of these direct costs during the delay period, as many patients visit ambulatory care multiple times between the time of initial symptom onset and the time of diagnosis. Ambulatory visits contributed for about 59.1% of total endometriosis-related costs, and researchers concluded that endometriosis-related costs were nearly twice as high in patients with intermediate and long diagnostic delays in comparison to those with shorter delays prior to a diagnosis of endometriosis [58]. Soliman et al. [61] looked at healthcare resource utilization during the year immediately prior to diagnosis and concluded that patients with endometriosis average 8 visits to physician offices, 1.8 visits to Ob/Gyn specialists, and 0.63 ER visits along with 20.2 prescriptions per patient in the 12-month period pre-diagnosis. All these outcomes were found to be significant when compared to utilization by matched controls. Fuldeore et al. [60] reported similar differences in emergency visits and physician visits for patients in the 5-year period before diagnosis. Patients with diagnostic delays therefore had a greater number of visits to emergency departments, visits to physicians, and visits to outpatient services which peaked in the year prior to diagnosis.

Pharmaceutical costs were also correlated with diagnostic delay and reported to average USD $568 for patients with short delays and USD $638 for those with long delays [58]. Baseline opioid prescription claims were significantly higher for cases (77.2%) than controls (40.6%) and close to double the number of claims was found for NSAIDs, antidepressants, and oestrogen/progestin CHCs amongst cases than controls. A lack of symptom control strategies before diagnosis along with long diagnostic delays contributes to increased prescription use for symptom management in patients with endometriosis, further contributing to direct costs associated

with this disease. This cost difference is likely to be an underestimate as many studies that explore costs associated with endometriosis in the pre-index period lack cost data on over-the-counter pain management, naturopathic remedies, and other self-management methods used by patients. Future studies should explore the frequency and cost of these alternative management methods used by patients prior to diagnosis to fully understand how diagnostic delays are contributing to increasing costs.

The need for earlier diagnosis and the impact of delays on increasing economic burden is heavily highlighted by these studies. Diagnostic delays contribute to both direct and indirect costs through a variety of mechanisms. Using clinical algorithms and a high index of clinical suspicion surrounding women with pelvic symptoms and infertility, we can improve the diagnostic delay seen in endometriosis (both for superficial lesions, endometriomas, and DIE) using other methods (i.e. ultrasonography) whilst also reducing costs associated with diagnosis.

Interestingly, some studies have looked at the all-cause healthcare costs and endometriosis-related healthcare costs in the year following diagnosis to understand if there is a change in expenditures. One such study [60] demonstrated the most significant difference in healthcare expenditures between endometriosis patients and controls occurred in the year immediately prior to diagnosis and the year after diagnosis. In specific, all-cause cost differences peaked in the first year following diagnosis concurrently with a rise in in-patient visits, out-patient visits, and emergency room visits. All-cause medical service costs in the first year following diagnosis averaged $12,005 for endometriosis patients compared to $3115 for controls. Patients with endometriosis averaged total healthcare costs of $13,199 in the first year following diagnosis, but in following years, the average annual total healthcare costs ranged between $3389 and $6720. Soliman et al. [61] reported that up to 60% of total healthcare costs for endometriosis patients occur in the first 3 months after diagnosis but appear to decline significantly following the first year of diagnosis [60, 62, 63]. Future studies should focus on evaluating whether a shorter diagnostic delay can result in a reduction of costs in the first year following diagnosis.

28.2.3 Potential Investigations to Aid the Diagnosis of Endometriosis

28.2.3.1 Endometriosis Biomarkers

Research has been conducted on the role of diagnostic biomarkers in the diagnostic pathway. Their potential application includes risk screening in stratification of patients who would benefit from further investigations. In this clinical scenario, having a negative test could avoid costly, invasive tests and unnecessary investigations, thereby relieving a large economic burden [3]. A positive test would accelerate time to treatment and decrease diagnostic delay [3]. Biomarkers may also have a role in estimating recurrence risks and could reduce the unnecessary follow-up care in low-risk patients [3]. Finally, a biomarker could help identify the best management option for patients and reduce costs associated with unnecessary/ineffective treatments.

Table 28.5 List of some biomarkers studied in endometriosis (Nisenblat et al. [64])

Biologic group	Biomarkers	Sensitivity	Specificity
Angiogenesis & growth factors	Vascular Endothelial Growth Factor	0.50–0.93	0.61–0.97
Apoptosis markers	Survivin	0.07	0.90
Cell adhesion molecules	Laminin-1	0.72	0.70
Hormonal markers	Prolactin	0.2–0.44	0.94–1.00
Immune and inflammatory markers	Anti-endometrial antibodies	0.81–1.00	0.39–0.75
	Tumour necrosis factor alpha	0.68–0.89	0.35–0.87
	White blood cells	0.64	0.54
	Interleukin-4	0.64	0.65
	Interleukin-6	0.63	0.69
Tumour markers	Cancer antigen 19.9 (CA-19.9)	0.36	0.87
	Cancer antigen 125 (CA-125)	0.40–0.73	0.64–0.91

Identifying reliable biomarkers for endometriosis is particularly challenging due to the need for stability across the hormonal changes instituted by the menstrual cycle, or on hormonal treatment [3]. A series of Cochrane reviews determined that despite some promising candidates, there is currently no single biomarker or panel that demonstrates clinical relevance [64]. Table 28.5 illustrates some of the most commonly studied blood biomarkers for endometriosis. Thus, despite the potential cost-saving measures that biomarkers could provide, the current literature suggests that most biomarkers are of limited diagnostic value.

28.2.3.2 Imaging

Reliable imaging methods with sufficient diagnostic power can be used as a non-invasive tool to accelerate the time to receive a diagnosis and to potentially alleviate the need for an invasive surgical diagnosis. Imaging methods can additionally be used as surgical planning tools to reduce the costs associated with unexpected surgical findings such as greater operative time, resources, and rate of complications [45]. The most commonly used imaging tools include ultrasonography (U/S) and MRI. Typically, transvaginal U/S is used as a first-line method because it is more easily accessible than MRI and can accurately identify endometriomas [3]. MRI is used as a second-line method to reliably identify DIE but is associated with greater costs, and it is typically not as widely available [3].

The utility of U/S is limited to specific findings in endometriosis. Transvaginal U/S shows clinical utility in differentiating endometriomas from other forms of ovarian cysts [65, 66] with a sensitivity and specificity of 0.93 (95% CI 0.87–0.99) and 0.96 (95% CI 0.69–0.89), respectively [45, 48, 65, 66]. Dynamic markers such as the negative sliding-sign representing immobility of pelvic organs can also provide information on severe endometriotic adhesions and advanced-stage disease [3, 66]. For DIE, transvaginal ultrasound has been shown to have a sensitivity of 0.79 and specificity of 0.94 [45]. U/S is also unreliable in detecting pelvic endometriosis with a sensitivity of 0.65 and specificity of 0.95 [45]. Despite these values, there is great variability of U/S diagnostic ability between providers based on their level of experience. Studies report a sensitivity of 0.81 to 0.91 and specificity of 0.97 to 0.98

when ultrasonography was performed by an experienced specialist to diagnose DIE [67, 68]. As a result, normal findings on U/S does not rule out endometriosis in the presence of clinical symptoms due to the questionable diagnostic power of U/S especially for superficial implants, and its dependence on experienced clinicians.

MRI is not routinely used as the standard of care in the diagnostic pathway due to the high cost and limited accessibility. A Cochrane Database Review [45] showed that MRI was highly sensitive and specific for the detection of endometriomas at 0.95 (95% CI 0.90–1.00) and 0.91 (95% CI 0.86–0.97), respectively. Kinkel et al. [69] reported that while MRI is superior to U/S in detecting small endometriotic lesions, it still lacks reliability for superficial endometriosis with a sensitivity of 0.79 and specificity of 0.72. For DIE, the sensitivity is higher (0.94) with MRI, but specificity remains low (0.77) [45]. The majority of studies examining MRI in the diagnosis of endometriosis are limited by their small numbers and varying methodological quality, demonstrating a need for further research in this field [45].

Superficial and peritoneal endometriosis poses an interesting problem to clinicians as it remains highly undetectable to assess using non-invasive diagnostic methods [45, 64, 70] and largely depends on diagnostic laparoscopy to visualize [70]. Recently, Leonardi et al. [70] tested the diagnostic utility of a novel transvaginal U/S procedure called saline-infusion sonoPODography (SPG) for visualizing superficial endometriosis. The diagnostic accuracy of SPG for detecting superficial endometriosis was evaluated against direct visualization at laparoscopy and histology. For all participants, SPG had a sensitivity of 64.9% and specificity of 100.0%, and amongst participants without DIE or ovarian endometriomas or Pouch of Douglas obliteration, SPG had a sensitivity of 77.7% and specificity of 100.0%. For those with isolated superficial endometriosis, the overall accuracy of SPG for direct visualization of superficial endometriosis was 80.0%. This method shows promise in investigating endometriosis in patients without DIE, ovarian endometriomas, or Pouch of Douglas obliteration who present with chronic pain and infertility problems.

Thus, while imaging methods may have the potential to reduce the costs and invasive nature associated with the surgical diagnosis of endometriosis, its utility is predominately in assessing endometriomas and DIE. Currently, the field lacks a cost analysis on imaging methods in comparison to laparoscopy for diagnosis, but future research should survey the cost difference and how triaging with imaging can reduce both direct and indirect costs associated with diagnostic delays.

28.3 Costs Associated with the Treatment of Endometriosis

28.3.1 How Is Endometriosis Treated?

Treatments for endometriosis pose a substantial economic burden on patients and healthcare systems. Currently, the aims of therapy are to manage symptoms and reduce the presence and growth of extra-uterine endometriotic tissue. Treatment

options primarily rely on medical or surgical intervention [2]. The type of treatment is selected based on the patient profile, disease location, severity, therapeutic goals, and desire for fertility. Early treatment has been shown to improve pain levels, quality of life, and daily functioning [71]. However, diagnostic delays significantly impede the ability to treat patients earlier and additionally contribute to increased costs in treatment.

The medical or surgical treatment options are thought to manage symptoms through reduction of inflammatory mechanisms and damage to nearby organs and tissues [72]. Currently, the mainstay of medical treatments are hormonal options [3]: CHCs, progestins, and gonadotropin-releasing hormone (GnRH) agonists and antagonists, as demonstrated in Table 28.6 [73]. While these treatments work to suppress oestrogen-induced growth of endometriotic tissue and relieve pain symptoms, they are each also associated with side effects [3, 73] and are not helpful when conception is a goal of treatment.

Table 28.6 Medical therapies for endometriosis

Drug category	Drug name	FDA-approved use
Combined hormone contraceptives (CHCs)	Monophasic oestrogen-progestin	FDA-approved treatment for endometriosis but may cause breakthrough bleeding
Gonadotropin-releasing hormone agonists (GnRH agonists)	Leuprolide depot	FDA-approved treatment for endometriosis but may cause decreased bone density
	Goserelin	
	Nafarelin	
Progestin-only contraceptives	Etonogestrel-releasing implant	Not FDA approved for treatment of endometriosis
	Norethindrone acetate	FDA-approved treatment for endometriosis
	Dienogest	Not FDA approved for treatment of endometriosis
	Depot medroxyprogesterone acetate (DMPA)	FDA-approved treatment for endometriosis but bone density loss is a concern with long-term use
	Levonorgestrel-releasing IUD	Not FDA approved for treatment of endometriosis but shown to be effective in reducing endometriosis-associated pain
Aromatase inhibitors	Letrozole	Not FDA approved for treatment of endometriosis and should be combined with CHCs, progestins, or GnRH agonists to prevent ovarian cyst development
	Anastrozole	
Oral gonadotrophin-releasing hormone antagonists	Elagolix	Not FDA approved for treatment of endometriosis and may cause lipid abnormalities and bone density loss
Selective progesterone receptor modulators	Mifepristone	Not FDA approved for treatment of endometriosis
	Ulipristal acetate	
Androgenic steroids	Danazol	FDA-approved treatment for endometriosis but seldom used due to undesirable androgenic side effects (i.e. acne, hirsutism)

Reference: [1]

The extent of surgical management depends on the goal of treatment. When fertility preservation is a primary goal, patients can undergo laparoscopic removal of endometriotic lesions through excision, cautery, or laser to improve the success of assisted-reproductive technologies [1]. When fertility preservation is not a concern, surgery can also concurrently include hysterectomy with or without bilateral salpingo-oophorectomy [1, 74], as this may reduce the risk of recurrent disease [75]. However, surgical complications and longer recovery times are associated with higher healthcare costs, poorer quality of life, and delayed return to employment.

Due to the chronic nature of the disease, endometriosis often requires long-term management depending on the patient's age, desire for conception, and disease severity. This section will focus on evaluating the costs associated with the various management options available to patients with endometriosis. It will also evaluate whether economic savings can be attributed to non-surgical approaches to care in primary care settings, while accounting for recurrence risk and associated complications.

Management for endometriosis is typically built on a "step-up" approach where patients are started on first-line therapies before progressing to more expensive options with higher risks of complications. This strategy is based on safety profile, cost-effectiveness, and patient-specific factors [76] as it limits the number of individuals who are placed on expensive medical therapy or who undergo surgery. Studies have shown that up to 75% of patients can receive effective symptom control from first-line therapy options including continuous use of CHC or progestins, thereby reducing the need for further treatment or surgery [76]. Surgical interventions such as excision or cautery of endometriosis or hysterectomy are typically reserved for patients who have not significantly improved with medical therapy or who have contraindications for medical options [77]. There is also evidence that a multidisciplinary approach with specific symptoms such as chronic pelvic pain is highly effective in conjunction with either medical or surgical management [78]. This hierarchical model for symptom management in endometriosis promotes the use of widely tolerated, low-risk therapies before escalating to the use of more invasive, riskier options.

28.3.2 Cost of Medical Treatments for Endometriosis

Patients who are medically treated for endometriosis suffer from high out-of-pocket prescription costs. Average annual costs range from USD $478 to $953 for controls without endometriosis compared to USD $608 to $1444 for patients with endometriosis [60]. The higher costs likely reflect the need for hormonal therapies such as CHCs, progestins, GnRH agonists and antagonists, in addition to the cost of analgesics. Many also use more than one medication at any given time for endometriosis symptoms, which can contribute to pill burden in addition to financial burden [32].

Several studies have contrasted costs for commonly prescribed medical treatments to determine the most cost-effective options with no clear result. A Scottish cost analysis [79] demonstrated that expectant management costs less at USD $697

compared to medical therapy at USD $1162 over the course of 6 months without significant differences in clinical and health outcomes [31, 79]. This conflicts with a decision analytic model suggesting that hormonal therapies were less expensive and provided more quality-adjusted life years in comparison to expectant treatment only with analgesics [80]. The increased costs associated with expectant management is attributed to increased healthcare utilization rates. Patients who exclusively used analgesics for symptom management had more frequent visits to their general practitioner in comparison to those using hormonal treatments [80]. In the UK, Pearson et al. [81] compared costs for 6 months of treatment on various medications for endometriosis. Treating patients with CHCs and progestins cost USD $8 and USD $11–$18, respectively, over 6 months [31, 81]. GnRH agonists, however, amounted to USD $1145 over the same period [31, 81]. Currently, the evidence comparing GnRH agonists to CHCs and progestins has demonstrated that there is limited utility and cost-effectiveness in using GnRH agonists as first-line treatments. Guzick et al. [82] demonstrated that there was no significant reduction in pain symptoms between patients administered a GnRH agonist and those using CHCs. Furthermore, the cost of treating patients for 48 weeks with the GnRH agonist was USD $8006 compared to USD $454 for CHCs. Due to the lack of data demonstrating significant improvements in symptoms, GnRH agonists have been commonly used as second-line treatments for patients who do not respond to CHCs or progestins or for those in which the former is contraindicated.

Many studies have also tried to draw cost comparisons between medical and surgical options. Empirical therapy with GnRH agonists has been shown to be less costly than surgical options when managing chronic pelvic pain in patients with endometriosis [83, 84]. A treatment protocol using a GnRH agonist as empirical therapy for endometriosis [85] and laparoscopy only for refractory cases projected cost savings of US $62,800 for the 22 patients enrolled in this trial. Although the upfront cost of GnRH agonists is significantly less than surgery [31, 83, 84], the reported 50% recurrence rate following treatment cessation should not be discounted [83]. Future research should explore the patient and disease factors of those who undergo surgery as a result of symptom recurrence once GnRH agonist therapy is terminated. This may help identify women who are better suited for surgery as opposed to GnRH agonist therapy earlier.

Currently, there is plenty of debate surrounding the cost-effectiveness of medical therapy in comparison to surgical intervention for patients that are appropriate candidates for both.

While there are reduced upfront costs for medical management compared to surgical management, it is important to consider side-effect profiles for medical therapies in addition to the financial burden of long-term medical management. At present, there are not enough high-quality studies to determine whether medical therapy is more cost-effective than surgery, given the high rates of symptom recurrence and potential need for surgical management following the end of the treatment course. There is also a lack of long-term prospective data describing the clinical efficacy of medical therapy in reducing recurrence rates and prevention of surgical intervention during the life course of a patient. These unanswered clinical

questions pose significant barriers in the development of cost-effectiveness models that can assist in the production of clinical guidelines.

28.3.3 Costs Associated with Surgical Interventions for Endometriosis

Surgical treatments are often used for patients who are non-responders to medical therapy or for whom hormonal medications are contraindicated [86]. There are many surgical options available, and associated costs vary depending on the type of surgery, length of in-hospital stays, and risk of complications. Currently, laparoscopic surgery is favoured over laparotomy due to shorter recovery times and lower risk of complications [63].

Approximately 65.5% of patients diagnosed with endometriosis will undergo surgery within 1 year of their diagnosis as opposed to 1.5% of controls [63]. An international, multicentre study [32] determined that about 29% of endometriosis-specific healthcare costs are due to surgery. In Canada, hysterectomy accounted for about 30% of all surgical procedures for endometriosis patients. Hospital admissions and surgical procedures represented about 53% of total hospital-associated costs for endometriosis [87]. This comes at a significant cost burden as multiple studies have consistently demonstrated greater upfront direct costs for surgical management compared to medical management [83, 84, 88]. This section will explore the various costs associated with surgical methods and the many drivers of high costs.

28.3.3.1 Cost Differences Between Surgical Procedures

The choice between surgical procedures tends to vary based on patient preference, disease severity, and the desire to maintain fertility. For women who are looking to conceive, fertility-sparing conservative surgery such as laparoscopic excision, cautery, or laser of endometriotic lesions is appropriate [18]. The addition of hysterectomy with or without salpingo-oophorectomy is reserved for patients who do not desire fertility [86, 89]. For hysterectomy, costs also vary based on the surgical technique which can include laparotomy, vaginal, laparoscopy, or a combination of the above [90, 91]. Choice of technique depends on patient factors, disease severity, and surgeon comfort [74].

Fuldeore et al. [63] explored cost estimates for various surgical interventions and noted surgeries requiring hospital admissions, such as hysterectomies, were significantly more costly compared to procedures which usually took place in out-patient settings. In the USA, endometriosis-related surgical procedures had an average length of stay between 1.5 and 2.8 days, with longer stays associated with more invasive procedures such as laparotomy (2.33 days), abdominal hysterectomy (2.59 days), and hysterectomy with oophorectomy (2.81 days) [63]. It is now generally accepted that laparoscopic technique is associated with shorter hospital stay, reduced morbidity, and faster recovery compared to laparotomy for similar procedures [35]. One US study reported total direct costs of USD $3271 per patient in the laparoscopy group and USD $7075 per patient in the laparotomy group [35].

Robotic surgery in endometriosis has also gained popularity in recent years as an alternative method to standard laparoscopy. However, systematic reviews have demonstrated that robotic surgery has minimal additional benefits and is associated with increased expenditures and increased procedure length per patient [92, 93]. A randomized controlled trial performed in patients with endometriosis compared the use of conventional laparoscopy and robotic surgery and found that both methods had comparable clinical outcomes and improvement to quality of life [94]. Given the lack of significant advantages in using robotic methods over traditional laparoscopy, it is important to consider costs, accessibility, and economic burden to the healthcare system when opting to use robotic surgery.

Studies have also demonstrated that surgical treatment for endometriosis is costlier than the equivalent procedure for another benign gynaecologic cause. A Canadian study reported that the total hospital-related costs for all surgical interventions relating to endometriosis cost CAD $152,206,977 from 2008 to 2013 [87]. Hysterectomy for endometriosis carried the greatest cost burden, costing the public-payer system close to CAD $55,034,511, whereas ovarian endometriosis costs approximately CAD $45,230,906. On a case-by-case basis, non-hysterectomy surgical procedures for treating ovarian endometriosis cost CAD $3224, while hysterectomy for endometriosis costs CAD $2356 [87].

The potential for out-patient procedures also creates an area for potential healthcare savings. Out-patient hysterectomy procedures are now increasingly favoured over in-patient hysterectomy procedures due to the reduction with length of stay and subsequent cost savings. The increasing uptake of Enhanced Recovery After Surgery pathways for the standardization and optimization of peri-operative care has also been shown to reduce the cost burden in gynaecological procedures [95]. In conjunction, these studies demonstrate the large financial burden placed on individuals and healthcare systems when treating endometriosis surgically and brings into question the future of sustainable public healthcare systems with increasing costs for surgical interventions in settings with finite resources.

28.3.3.2 Cost Differences Between Medical and Surgical Treatment of Endometriosis

Soliman et al. [96] estimated that total direct healthcare costs for patients who underwent surgery was $19,203 per patient annually, whereas those who did not undergo surgery had average total direct healthcare costs of $6365 per patient annually [96]. This could be attributed to the increased healthcare resource utilization by surgical patients the following year after surgery [96]. In-hospital admissions were the main contributor to costs in the surgical cohort—which approximated 68.8% of the cost—followed by pharmaceutical claims. With an increasing number of practitioners opting for less invasive surgical options such as laparoscopy, the direct costs associated with the surgical procedure, length of stay, and in-hospital admissions can be controlled to various degrees. Cost-control measures could explore reducing this length of stay by choosing more minimally invasive approaches such as laparoscopy instead of laparotomy [87] and favouring out-patient pathways. The impact

of indirect costs such as work absence and short-term disability due to surgery was also higher in patients who underwent surgery.

28.3.3.3 Hospital Admissions

In-patient stays and hospital admissions associated with endometriosis are large cost drivers for the healthcare system. In Canada, total hospital costs for endometriosis-related hospital admissions resulted in CAD $30.44 million annually (US $29.56 million), and on average, it costs CAD $3237 (US $3134) per admitted patient case [87]. In 2002, about $22 billion was spent on endometriosis-related costs in the USA of which $14.5 billion was spent on hospital care with admissions as the paramount cost driver [31]. In fact, endometriosis-related hospitalizations are the third leading cause of gynaecologic hospitalizations in the USA [97]. Interestingly, researchers found that different forms of endometriosis are associated with varying degrees of cost. Uterine endometriosis and ovarian endometriosis accounted for the bulk of hospital admissions, with uterine endometriosis being the most expensive to treat [CAD $4137 (US $4017) per case] followed by ovarian endometriosis [CAD $3506 (US $3404) per case].

28.3.3.4 Risk of Disease Recurrence

While surgical interventions can provide significant symptom relief and improvements in quality-adjusted life years, they are costly and have varying degrees of symptom recurrence associated with them. Fertility-sparing surgical interventions can improve fertility and reduce physical disease, but up to half of surgical patients will have recurrence at 2 to 5 years post-surgery [98, 99]. There is conflicting literature regarding rates of recurrence. Guo et al. [98] suggest that post-operative symptom recurrence can occur at a rate of 10% annually, whereas Sutton et al. [100] reported recurrence in approximately 44% of patients within 1 year of surgery. Similarly, Hornstein et al. [101] reported a 51% recurrence rate in patients who underwent laser ablation of endometriotic lesions. Although recurrence is more infrequent with hysterectomy and bilateral salpingo-oophorectomy [75], there is still a 5–10% probability that patients may continue to experience symptoms post-surgery [102]. The risk of recurrence carries negative impacts on patients' quality of life as well as consequences on healthcare expenditures. Patients who experience symptom recurrence may elect to undergo additional surgical procedures or may need to be placed on post-operative medical therapy to help control symptoms—both of which lead to further increasing costs in managing endometriosis.

There is some suggestion of higher symptom recurrence associated with medical management when compared to surgical treatment [102, 103]. Not many studies have evaluated recurrence rates with medical therapies, but one study reported recurrence rates at 1-year post-therapy cessation of 13% for patients on leuprolide acetate and 12% for goserelin acetate [104]. Another study [105] compared aromatase inhibitors (letrozole) with GnRH agonists (triptorelin) after a 2-month therapy period and found that the group on letrozole had a recurrence rate of 6.4%, whereas the group on triptorelin had a recurrence rate of 5%; however, there was no statistical significance between these therapies in symptom recurrence. A study exploring

the benefits of nafarelin, another GnRH agonist, has also shown 26% of patients on either a 3- or 6-month therapy schedule experienced symptom recurrence [106].

Randomized controlled trials have explored the use combining medical therapy post-operatively to help with symptom recurrence. Specifically, the post-operative use of a levonorgestrel-releasing intrauterine device (LNG-IUD) has been shown to be effective in reducing the recurrence of dysmenorrhoea [107, 108]. However, the LNG-IUD does not inhibit ovulation and is consequently less effective in preventing the recurrence of endometrioma formation [108]. Prior research has also reported that pre-menopausal patients who undergo more conservative surgical procedures with ovarian or uterine preservation are at a six times greater risk for undergoing repeat surgical procedures due to the higher probability of disease recurrence [109–111].

It is clear that the risk of recurrence remains significant in both medical and surgical interventions for endometriosis and pose additional costs for patients in whom symptoms or endometriotic implants recur post-surgery. Studies that evaluate surgical cost-efficacy and report on cost estimates should also include costs associated with the risk of recurrence stratified by type of medical management or surgical procedure.

28.3.3.5 Costs Associated with Treating Endometriosis-Related Infertility/Subfertility

The impact of endometriosis on fertility is well documented in the literature. Options for women trying to conceive range from expectant management, surgical excision of lesions, or assisted reproductive technologies (ART) [3]. Hormonal medical therapies are contraindicated in these patients as they often suppress ovulation. Patients who are likely to succeed with expectant management often are younger, have normal ovarian reserve, regular ovulation, and uterine tube patency [3]. Older patients with more extensive disease are often treated with surgical therapy or ART [3].

While surgery may help stabilize the reproductive architecture and correct anatomical distortions from endometriotic implants, there is a correlation between surgical therapy and decreased ovarian reserve [3]. Patients with mild to moderate disease may benefit from surgery to increase their chances of spontaneous conception [112]. However, the improvement in fecundity is minor at 8%, with only marginal improvements in spontaneous conception [3, 113, 114]. In patients with moderate to severe disease, the estimated surgical benefit is smaller due to the presence of tubal adhesions, and ART is more often recommended [115]. Overall, the clinical utility in surgery for fertility is limited, as 25 patients would need laparoscopic surgical management to achieve one more live birth when compared to expectant management [112, 113, 116].

Patients with normal ovarian reserve may be eligible for multiple ART options such as superovulation or intrauterine insemination [116] which is less costly than in vitro fertilization (IVF). However, there are minimal benefits to using this approach in patients with endometriosis [117, 118]. IVF has been more associated with successful rates of pregnancy in patients with endometriosis, especially for those with diminished ovarian reserve [74]. Prolonged treatment with hormonal

therapies such as GnRH agonists or CHCs has been shown to help improve pregnancy rates using ART [119, 120]. Outcomes using ART have also been shown to be superior to surgical therapy in patients with endometriosis to achieve conception [121].

The Endometriosis Fertility Index (EFI) has been used to predict the occurrence of spontaneous pregnancy following endometriosis surgery and plays an important role in helping physicians triage patients into expectant management or assisted reproductive technologies [122]. Ferrier et al. [122] conducted a cost-effectiveness analysis to determine the costs associated with different ART treatment pathways immediately after surgery for endometriosis-associated infertility. Specifically, they explored the use of the EFI to stratify patients and determine appropriate care pathways to study cost-effectiveness. Patients were channelled into three different care pathways to manage endometriosis-associated infertility using the EFI as a stratification tool: natural conception, immediate IVF-Intracytoplasmic sperm injection (IVF-ICSI), and delayed IVF-ICSI. The costs for patients who underwent IVF-ICSI amounted to €9509 per patient, €15,196 per pregnancy, and €18,235 per live birth with an incremental cost-effectiveness ratio of €31,469 per pregnancy over expectant management. Although immediate IVF-ICSI post-surgery is an appropriate method for attaining fertility in endometriosis patients, it presents significant costs for the healthcare system. Further research is needed in the role of expectant management for select patients after surgery (such as those with a good prognosis, normal ovarian reserve with high EFI score).

IVF, while demonstrating successful rates of conception in endometriosis patients, still poses a large financial burden on patients and healthcare systems. Apart from the costs associated with the procedure, there are also ancillary costs that are incurred by patients. These costs include medical costs, fertility counselling, time off work, and/or psychological support. Patients with diminished ovarian reserve often require egg donation which is also associated with significant logistical expenses incurred by the patient. A partially, publicly funded IVF model in Canada reported that 49% of patients still paid between CAD $5000 and CAD $10,000 in ancillary costs, with 18% paying between CAD $10,000 and CAD $20,000 to undergo IVF [123]. Collins [124] in 2002 found that the average cost per IVF-ICSI cycle was around $9547 in the USA and $3518 in 25 countries around the world. In fact, IVF costs ranged from 10% of annual household expenditure in European countries to 25% in Canada and the USA [124]. These studies explicitly display the large financial burden placed on individual patients and healthcare systems as a result of treating infertility, and these costs are compounded by the ART that is often needed to attain a pregnancy in patients with endometriosis.

28.4 Indirect Costs Associated with Endometriosis

Although direct costs have often taken the spotlight in cost-efficacy literature, indirect costs are equally as important to account for when creating true cost analyses for disease burden. Indirect costs are often left out of these estimates because of the difficulty and large variability in quantifying these costs. This often arises due to a

large reliance on self-reported data to account for factors such as loss of work productivity, childcare, caregiver support as well as variable valuation of these factors [125]. The main demographic affected by endometriosis are of reproductive age, which constitutes the majority of working-age members of the population. In fact, patients between the ages of 18 and 44 years account for approximately 75% of all endometriosis hospital admissions [18]. In 2002, Simoens et al. [31] estimated the annual endometriosis-related healthcare cost burden in the USA to be close to $22 billion and 21% of this estimate ($4.7 billion) was due to indirect costs, mainly through a loss of productivity. In 2010, the annual societal burden of endometriosis in the USA was projected at $69.4 billion of which two-thirds was reportedly due to loss of productivity [32]. These studies demonstrate the significant role of indirect costs in the total economic burden of endometriosis.

28.4.1 What Are the Indirect Costs Associated with Work Absences and Productivity?

Work absences and productivity represent major contributors to the indirect costs associated with endometriosis. Missed hours of work annually due to endometriosis-related chronic pelvic pain range from 19.2 hours to 86.4 hours per patient [126, 127]. Mathias et al. [127] also noted that endometriosis caused patients to miss 1.6 hours of work every month in comparison to 0.05 hours missed by patients with other menstrual cycle–related diagnoses. Nnoaham et al. [10] showed that endometriosis resulted in equivalent work loss of approximately 6.4 hours per week due to presenteeism and 4.4 hours per week due to absenteeism across ten countries. In the USA, this would amount to approximately $3200 lost per year from absenteeism and $14,800 lost per year from presenteeism [10]. Levy et al. [128] quantified the loss of work productivity and leisure time costs to be close to $3854 per patient annually in Canada. It is evident from these studies that endometriosis-related pelvic pain severely impacts work productivity and patients' ability to maintain employment [129], thereby solidifying the further impact of endometriosis on economic burden.

There is also evidence that the work absences and productivity associated with endometriosis can have life-long negative effects. One matched case-control study demonstrated that women with endometriosis are significantly less likely to work in their desired profession, and more likely to consider health-related limitations in career choices, compared to a matched control group [130]. Similarly, those living with endometriosis can experience lower annual salary and salary growth compared to those without endometriosis [131]. The life-long cost implications are currently not well quantified in the literature.

28.4.2 What Are the Indirect Costs Associated with Surgery?

Surgical treatment plays a significant role in increasing indirect costs to patients. One study reported a productivity loss of $2236 per patient in the 6 months prior to surgery and $3686 in the 6 months post-surgery [132]. Indirect costs after surgery

may be attributable to longer recovery times, absences from work, and post-surgical pain. These findings are aligned with the idea that pelvic pain and disease severity are major drivers of work productivity loss for endometriosis patients [10]. Another study demonstrated that absence claims were higher in patients who underwent surgical treatment for endometriosis, resulting in a loss of income close to $6237 for those in the surgery cohort compared to $4781 for those who were not in the surgery cohort [96]. Absenteeism, short-term disability, and long-term disability were also all reported significantly higher in the surgery cohort [96].

28.4.3 Why Are Indirect Costs Important?

Indirect costs are important contributors to the overall financial burden of endometriosis on the individual, healthcare systems, and society. The majority of economic literature has focused on direct costs, largely due to the difficult nature of reliable valuation of factors such as presenteeism, the lack of self-report data, or an inconsistency in what qualifies as an indirect cost. Most of the indirect costs to date have focused on factors such as absence claims, work productivity, and unemployment. There is a clear lack of research focusing on indirect costs such as childcare and transportation, in addition to the difficulty in quantifying costs of social withdrawal, psychological impacts, and loss of leisure time.

Indirect costs play a large role in the economic burden of endometriosis. Understanding these factors can provide strategies to mitigate the substantial productivity losses arising from endometriosis-related symptoms. The diagnostic and treatment delays also play a role in exacerbating productivity losses. These intangible costs are equally as important to study given the multifaceted impacts of endometriosis on patients' lives and the life-long impacts this can have.

28.5 Conclusions

28.5.1 What Is the Global Economic Burden of Endometriosis?

This chapter has highlighted the direct and indirect costs associated with endometriosis and the many ways these costs contribute to the economic burden of many societies and healthcare systems. Although it is difficult to draw direct comparisons between the cost estimates due to inherent differences in healthcare system structures and regional practices, the large global economic burden remains consistent. The cost-efficacy of practice and policy guidelines on the diagnosis and treatment of endometriosis must be taken into account to ensure sustainability of national healthcare systems.

The current available data are limited as the national economic burden varies from country to country depending on population size and the local guidelines for clinical practice for endometriosis. Differences in reported endometriosis prevalence rates can further the variations in the subsequent estimated economic burden.

Table 28.7 National economic burden by country

Country	National annual economic burden	Type of costs accounted for
Germany [133]	€40,708,716	Direct costs from in-patient treatments for endometriosis
Austria [53]	€328 million	Direct and indirect costs
Canada [128]	$1.8 billion	Treatment costs, quality of life, work absenteeism, and caregiver time
Denmark [32]	€0.8 million	Costs associated with endometriosis-related symptoms
Switzerland [32]	€1.3 billion	
Hungary [32]	€1.6 billion	
Belgium [32]	€1.7 billion	
Netherlands [32]	€2.6 billion	
Italy [32]	€9.3 billion	
France [32]	€9.5 billion	
UK [32]	€9.9 billion	
Germany [32]	€12.5 billion	
USA [32]	€49.6 billion	

Table 28.7 illustrates the variability in national economic burdens per country. In Europe, economic burdens range from €3114 to €9872 [32, 53, 134, 135] per patient annually, whereas US numbers range from USD $8417 to $18,881 per patient annually [18, 60, 63]. Endometriosis-associated costs appear to be highest in the USA, and this theme recurs quite often in the literature [18, 32, 60, 63, 87, 96]. Both the direct and indirect costs associated with endometriosis need to be included in these national cost analyses to identify potential interventions that can target these large hidden cost drivers.

It is clear that endometriosis has a large stake in national expenditures for many healthcare systems around the globe. There is a strong need to reduce the diagnostic delay using more consistent guidelines, increased awareness amongst general practitioners, and more reliable diagnostic tools. Timely diagnosis would help reduce both the unnecessary healthcare expenses and the indirect costs associated with loss of productivity. More cost-effectiveness studies need to be conducted regarding the treatment of endometriosis and its risk of recurrence. Finally, to ensure that healthcare systems remain sustainable, rising costs related to endometriosis should be monitored and its contributing factors should be studied for cost-efficacy and global economic impacts.

28.5.2 Limitations and Future Directions

28.5.2.1 Lack of Control Groups

There are many limitations to the cost analyses referenced in this chapter. One of the largest criticisms surrounding cost-effectiveness studies is the lack of control groups and matched controls to draw adequate comparisons. Control groups help delineate

potential confounders, and a matched group of controls without endometriosis can help formulate better causal relationships about the economic burden of this disease on patients. A lack of control groups also biases cost estimates and makes it difficult for policy makers to understand the discrepancy in incurred costs for endometriosis patients compared to those living without endometriosis. Adequate control groups would also distinguish between costs incurred as a result of having endometriosis from costs incurred through endometriosis-related symptoms, such as pelvic pain and infertility, which are present in conditions outside of endometriosis [31]. This methodology would help better understand the costs arising from the disease itself as opposed to the related symptomatology.

28.5.2.2 Inclusion of Patient Profile Characteristics

Future studies should also attempt to understand how patient profile and disease characteristics impact endometriosis costs. Both direct and indirect costs may be influenced by patient factors and disease characteristics such as severity, symptoms, location, and type of endometriosis. Many studies did not list their patient profile or characterize individual disease, and this makes it difficult to generalize cost estimates to specific populations. This is especially relevant when comparing the heterogeneity of endometriosis, as more severe disease is likely to increase cost burden. There is also a lack of data focusing on endometriosis-related costs and economic burdens in Asian, Middle-Eastern, and African populations. Future research should focus on quantifying these costs in these populations and developing theoretical models to understand the global impact of endometriosis on health economics.

The presence of comorbidities is an important consideration when exploring costs associated with endometriosis as they ultimately inform treatment options and impact overall costs incurred. As endometriosis is commonly associated with other chronic pain disorders, its true economic burden may be underestimated when these comorbidities are not accounted for. Costs for comorbidities that are directly related to endometriosis should be included in cost analyses to capture the full spectrum of disease burden [33].

Another aspect that needs to be explored in cost estimates is the inclusion of suspected cases of endometriosis. Clinically suspected cases of endometriosis without histopathological diagnosis may benefit from inclusion in endometriosis studies to model the full extent of disease burden. These cases will provide valuable information regarding the true impact of the diagnostic delay and indirect costs such as productivity loss and unemployment. Inclusion of undiagnosed and misdiagnosed cases will also help explore costs incurred from unnecessary investigations and tests and multiple out-patient visits. Finally, many current studies tend to exclude adolescents and peri- or post-menopausal women and thereby, overlook the large costs specific to these groups. While the majority of endometriosis cases are in reproductive-age women [60], future studies should also explore hospitalizations for pelvic pain and endometriosis-related symptoms in women outside of this age range to accurately calculate cost estimates.

28.5.2.3 Costs Associated with Recurrence Risk

Despite its high prevalence, many studies do not account for costs following recurrence from cessation of medical therapy or post-surgery. Further research on the risk of recurrence could better estimate the costs associated with various risk factors to better understand their true effectiveness across a patient's life course. Recurrence rates and associated costs should also be assessed when conducting cost-effectiveness studies for various treatment interventions to be more reflective of the longitudinal and chronic nature of endometriosis.

28.5.2.4 Value-Based Care Studies

Future directions should also include the need for more value-based care studies on the impact of endometriosis expenditures [136]. Global guidelines for the diagnosis and treatment of endometriosis are inconsistent, producing a need for research that evaluates the merits of these varying interventions. These studies will help in reducing low-value care and unnecessary healthcare expenses. Value-based care studies should explore current screening, diagnostic options, and management options available to endometriosis patients to determine the optimal benefit associated with specific approaches to management. While it is difficult to draw parallels across different regions, there is utility to studying resource utilization rates to understand geographic variability in value-based care.

There is also a need for studies contrasting the cost-efficacy of different approaches to diagnosis and management. This will help policy makers stratify and prioritize diagnostic and treatment options while limiting the amount of unnecessary and costly tests and treatments. In particular, the cost-efficacy of medical versus surgical therapies need to be studied with a longitudinal approach across the lifespan of patients with endometriosis. Studies should aim to understand the utilization of healthcare resources, from the first initial visit with symptoms to the point of definitive diagnosis. There are usually multiple clinic and hospital visits with varying healthcare providers that occur during this window of time where many unnecessary tests are initiated in the pursuit of diagnosis. Similarly, the number of investigations and interventions from diagnosis to an improved quality of life need to be captured to study how patients with endometriosis utilize healthcare resources during their lifespan. To truly understand and help inform value-based care guidelines, unnecessary investigations and their utilization rates must be clearly studied. Furthermore, novel diagnostic tools and interventions should be assessed for their impact on reducing expenditures in conjunction with their ability to diagnose and treat endometriosis while improving quality of life for patients.

More comprehensive studies which document cost estimates, especially with regard to the direct and indirect costs of IVF and other forms of ART are needed. The literature is currently limited in identifying whether immediate ART post-surgery or delayed ART with expectant management is more cost-effective for treating fertility. Future research should also explore the overall financial burden related to treating endometriosis-associated infertility and subfertility, by calculating the

total healthcare costs required to achieve a successful live birth per patient [18] and the number needed to treat to attain one more pregnancy.

28.5.2.5 Lack of Studies Quantifying Non-Healthcare Costs and Indirect Costs

The lack of research outlining the full spectrum of indirect costs associated with endometriosis is alarming and points toward conservative estimates of national economic burdens. The true financial impact of the diagnostic delay for endometriosis cannot be determined without the inclusion of indirect costs such as productivity loss and work absences during this period. Disease severity and level of impairment should also be studied to understand correlations between these factors and their impact on quality of life. Given that the majority of endometriosis patients are in the workforce, cost estimates and economic burden must take into account the various indirect costs. Of the studies that explore indirect costs, many studies focus on factors such as presenteeism, absenteeism, unemployment, and work productivity to quantify lost income. There is a lack of studies focusing on other forms of indirect costs such as caregiver support, transportation costs to appointments, and childcare costs. Other non-healthcare costs are also not studied such as the use of alternative medicine and supplemental care such as physiotherapy, chiropractic, or lifestyle interventions. Future studies need to focus on identifying and quantifying non-healthcare related costs and indirect costs.

28.5.3 Concluding Remarks

Healthcare resources are finite and given the current global climate, healthcare systems need to consider sustainability when faced with growing expenditures and disease burden. The cost-effectiveness of diagnostic procedures and treatments must be systematically reviewed to ensure that healthcare systems appropriately allocate care that is high impact, especially in publicly funded or administered models of care. This chapter highlights the enormous global economic burden associated with endometriosis, which likely remains a conservative estimate of the real costs posed to individuals, health systems, and society. There is substantial healthcare resource utilization which contributes to the economic burden of endometriosis, and this problem is compounded by the propensity of patients to undergo multiple unnecessary tests and interventions across a variety of settings before obtaining an appropriate diagnosis or treatment. Enormous endometriosis-related costs without the proportionate improvements in health outcomes threaten the sustainability of national healthcare systems. The numerous factors contributing to these rising costs have been explored thoroughly in this chapter, and this knowledge will help guide future healthcare providers, hospital administrators, and policy makers in curtailing expenditures while balancing patient outcomes.

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