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The Handbook of Contraception

Evidence Based Practice Recommendations and Rationales

Third Edition

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This book is dedicated to my mentor Dr. Daniel Mishell, Jr. who led the field of contraception for over 40 years. For most of my training and early career, Dr. Mishell was editor of the leading journal Contraception. His major funding came from the World Health Organization, the Population Council, and the Ford Foundation. I worked for him for several years in the only clinical research and training center in human reproduction in the USA that was one of only 16 in the world.

In the 1960s, Dr. Mishell performed the first immunoassays of human chorionic gonadotrophin in urine and serum, which was the breakthrough that lead to the first pregnancy tests in the USA not involving animals such as rabbits or frogs. He was the first to describe the midcycle luteinizing hormone peak in the middle of the menstrual cycle which eventually led to the home ovulation test that allows women who want to become pregnant to determine when they are most fertile.

He conducted the first study using a steroid-impregnated vaginal ring for contraception and conducted pivotal studies on the levonorgestrel-releasing IUD, the copper IUD, the levonorgestrel-releasing contraceptive implants, and many new birth control pills. Importantly, Dr. Mishell demonstrated that a monofilament tail-string of an IUD does not cause bacteria to enter the endometrial cavity and that the major mechanisms of action of the IUDs occurs before fertilization.

Thank you Dr. Mishell for leading the field, developing and advancing so many contraceptive methods, and for bringing me and so many others into the "cutting edge" of advancements in contraceptive technology. You will long be remembered with gratitude and awe.

Donna Shoupe, M.D., M.B.A.

Foreword

In this day and age, it is quite reasonable to ask: why update any textbook? Who reads textbooks these days? After all, everything is available online, easily accessible whenever you have a question. This is especially true for contraception, where the CDC has developed and published the most current evidence-based recommendations for identifying candidates for each of the contraceptive options (US MEC) and for establishing practices that streamline women's access to each of the methods and provide guidance for managing common side effects (SPR). And they have even put it into an easily accessible, downloadable free app!

Experience tells us that many clinicians in different practice settings appreciate the direct answers they get consulting these resources, but they often desire more detailed information to better understand the evidence and reasoning underlying those bottom-line recommendations. And they want all that in one easily accessible site. Hence, the demand for quality textbooks remains alive and well.

Historically, there have been three major US family planning textbooks, each basing its recommendations on the most currently available evidence but meeting the needs of different audiences. Robert Hatcher published his first slender edition of *Contraceptive Technology* in 1971; the 21st edition of that text (much bigger now with 989 numbered pages) was released in 2018. This text is generally used by advance practice nurses, PAs, and primary care providers because it adds to the core CDC materials more practical tips and detailed information to help in patient counseling.

The 6th edition of Philip Darney and Leon Speroff's classic text, *A Clinical Guide for Contraception,* has recently been published. Incorporating considerable additional information about the scientific underpinnings of each method and supplying important historical perspectives, this text has generally been relied upon by contraceptive specialists.

In between those two classics emerged the first edition of this text*, The Handbook of Contraception* by Donna Shoupe, in 2006. It was designed to be most useful to primary care providers who serve the reproductive health needs of both men and women. Initially Donna Shoupe was inspired by the pioneering work her chair, Daniel R. Mishell. Mishell was in the forefront of contraceptive development and

testing for decades. His creation and consistent editing of the respected *Journal Contraception* allowed work of innovators around the world to be widely disseminated.

The Handbook of Contraception has always provided state-of-art information for practitioners in a very readable text that clearly highlights prominent take-home messages and uses cases to illustrate not only the basic principles but also important variations and exceptions to the rules. Dr. Shoupe created and edits a companion journal – the online *Journal of Contraception and Reproductive Health* – with a broad clinical perspective that explores issues that arise in different practice settings around the world.

Carrying on the theme of increasing access to information, this third edition of *The Handbook of Contraception* is being made available online, either in toto or by individual chapter. Readers can order only those chapters that apply to their practice or they can have all the chapters to appreciate the full range of family planning options and applications.

The third edition of *The Handbook of Contraception* consists of two parts. The first part includes individual chapters on each of the types of reversible and irreversible contraception. The second part focuses on meeting the contraceptive needs of different groups of patients – different age groups, different hormonal statuses, and different medical challenges. Areas that have unanswered questions are highlighted in a chapter on controversies in contraception. All the chapters are authored by some of the most experienced experts as well as emerging thought leaders in the field. As such, the perspectives of all ages from baby boomers to millennials are reflected in this work.

The guiding force in this work was its editor, Donna Shoupe, MD, whose enthusiasm and palpable delight for this endeavor was contagious. Always open to new ideas, she expanded the content of the book and made it even more relevant to both new readers and those who had seen earlier editions. She maintained the format that makes this manuscript so easy to scan and embraced the elasticity and flexibility of this new production model that rejects the all or nothing of the traditional textbook and permits readers to construct the book that meets their needs by selecting the chapter(s) they need.

I invite you to build your book, use it, and enjoy it.

Anita

Preface

The Handbook of Contraception Third Edition is a comprehensive textbook that is designed to guide management and understanding of the many complex issues surrounding contraception. This book addresses each of the currently available contraceptive methods available in the United States in multiple ways. The first section of the book begins with an overall chapter on contraceptive effectiveness. The following chapters in the first section of the book individually address combination contraceptive pills, progestin-only contraceptive pills, the contraceptive patch, the contraceptive vaginal ring, injectable progestins options, the contraceptive implant, non-hormonal and hormonal IUDs, barrier methods, emergency contraception, female tubal sterilization, behavior method and finally vasectomy. These chapters on individual methods address risks and benefits of each method, good and bad candidates, side effects, initiation issues, and counseling points. In each chapter the new related products on the near horizon are also introduced.

The second part of the book entitled Evidence-Based Practice Guidelines addresses clinical issues in choosing the right contraceptive methods for women in general or those with common specific medical conditions. The first chapter in this section addresses healthy reproductive aged women in general, women with obesity, those with androgen excess or excess bleeding, and contraception in adolescents and perimenopausal or postpartum women. Complete chapters on postpartum candidates, perimenopausal women, and adolescents follow. The final chapter addresses controversies in contraception.

The authors and editor of this Handbook hope that this book will help clinicians gain more expertise in counseling their patients so that as a team they can decide on an effective, safe, and convenient contraceptive option that will be used continuously and correctly.

Los Angeles, CA, USA — Donna Shoupe

Acknowledgments

Thanks to all the hardworking and outstanding authors that contributed to this book. As each chapter was delivered to me, I continued to learn so much and was more and more delighted with each submission. The best edition yet!!! Each author shared their valuable clinical experience and backed it up with important studies, common practices, and national and international society recommendations. I would especially like to thank Anita Nelson who was not only an author but also contributed her guidance through the Family Planning Division at USC (plus also wrote the Foreword!) The combined team contributed heavily to this new edition.

Thanks also to Springer and their representatives, especially Abha Krishna, who worked tirelessly with me and the authors. Finally, a salute to the healthcare workers on the front line who face the issues discussed in this edition on a daily basis.

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Part I
Prescribing Contraceptive Methods

Chapter 1
Contraceptive Effectiveness

Michael Awadalla

Introduction

Both women and men consider effectiveness one of the most important factors when choosing a contraceptive method [1]. This makes an understanding of contraceptive effectiveness essential for healthcare providers when counseling patients regarding contraceptive options. Maintaining an accurate and up-to-date knowledge base is complicated by a number of factors including a growing list of contraceptive methods along with large differences in study methodology and user characteristics. This chapter reviews the factors influencing contraceptive failure rates along with current estimates of contraceptive failure rates with the aim of improving the knowledge base of healthcare providers.

What Is the Difference Between Effectiveness and Efficacy?

Contraceptive effectiveness is the reduction in the monthly rate of conception (fecundability) that results from typical use of that contraceptive and can be calculated as follows [2]:

$$\text{Reduction in rate of conception} = 1 - \frac{\text{Observed conceptions}}{\text{Expected conceptions}}$$

For example, if the monthly rate of conception is 20% in a group of patients then a contraceptive that is 95% effective would reduce the monthly pregnancy rate in that

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group to 1%. Contraceptive effectiveness is based on typical use which includes inconsistent and incorrect use. Contraceptive efficacy is the is the reduction in the monthly rate of conception that results from perfect use of that contraceptive and is equal to or greater than the contraceptive effectiveness. If perfect use of a contraceptive reduced the monthly conception rate from 20% to 0.5% then the contraceptive efficacy would be 97.5%. Large differences between effectiveness and efficacy indicate that a method is difficult to use or remember to use as is the case with contraceptive pills. Long-acting methods such as intrauterine devices, the contraceptive implant, and surgical sterilization typically have very similar effectiveness and efficacy.

Both contraceptive effectiveness and efficacy are difficult to determine accurately for four main reasons. First of all, the monthly rate of conception for a given patient population depends on many factors such as age and coital frequency that are impossible to determine precisely. Second, "method failures" which result in accidental pregnancies conceived during perfect contraceptive use can be difficult to differentiate from "user failures" which result in accidental pregnancies during imperfect use [2]. Third, patients participating in a prospective research study may be more consistent in their contraceptive use than patients who are not participating in a research study [3]. This would result in a study reporting greater contraceptive effectiveness than seen in patients outside of a research setting. Lastly, interpreting outcomes is difficult when patients discontinue a contraceptive method or become lost to follow-up during a study.

Measuring Contraceptive Effectiveness and Efficacy

In clinical practice, simply measuring rates of contraception failure (pregnancy) over a period of time for both typical and perfect contraceptive method use is more practical than trying to compare the rates to those of a similar patient population not taking contraception. Instead of measuring contraceptive effectiveness, the rate of pregnancy during typical contraceptive method use is measured. Instead of measuring efficacy, the rate of pregnancy during perfect contraceptive method use is measured.

Traditionally, contraceptive failure has been measured using the Pearl Index [4]. The Pearl Index is easy to calculate and it is the required method for reporting contraceptive efficacy to the Food and Drug Administration when applying for new drug approval. The Pearl Index is the number of failures (unintended pregnancies) per 100 woman-years of contraceptive use. The numerator is the number of unintended pregnancies and the denominator is the cumulative number of months of contraceptive exposure from initiation of the contraceptive method until the end of the study, discontinuation of the method, or pregnancy. The result is multiplied by 1200 to account for the fact that there are 12 months in a year and that by convention the Pearl Index looks at rates per 100 years.

$$\text{Pearl Index} = \frac{\text{Number of unintended pregnancies}}{\text{Number of months of contraceptive exposure}} * \left(\frac{12\,\text{months}}{1\,\text{year}} \right) * 100\,\text{years}$$

Despite its simplicity and ease of use, the Pearl Index has significant limitations. The most significant limitation of the Pearl Index is that it views contraception as an unchanging state rather than a fluid process. If a group of women using a contraceptive method all had the same probability of having an accidental pregnancy that was fixed over time, the Pearl Index would be an accurate reflection of contraceptive efficacy. However, we know that each woman's underlying fertility is different and each woman's motivation and ability to consistently and correctly use a contraceptive method can vary significantly. Women at higher risk of pregnancy due to greater fecundability, improper use of contraceptives, more frequent intercourse, or younger age are much more likely to become pregnant compared to those women at low risk of pregnancy. A study population containing a large percentage of these fertile women will often have a higher failure rate than a study population consisting of women with lower fertility. Additionally, over time, women with contraceptive failures are removed from the ongoing analysis and the remaining women will have a lower rate of contraceptive failure than the initial group.

Therefore, when comparing the Pearl Index for contraceptive methods, it is incorrect to compare studies of different durations because the longer the study, the lower the Pearl Index, even if the inherent efficacy rate between two methods is the same [2, 3].

Another limitation of the Pearl Index is that, although studies attempt to separate method failures from user failures, both failure rates are often underestimated due to incorrect methods of calculation. Method failures by definition can only occur during cycles of perfect contraceptive use. User failures can only occur during cycles of imperfect contraceptive use. When determining the contraceptive failure rate for method failures, the denominator should be restricted to months or cycles of perfect contraceptive use. Likewise, when determining the contraceptive failure rate for user failures, the denominator should be restricted to months or cycles of imperfect contraceptive use. However, this is rarely done and therefore the denominator for both calculations often includes all women and is therefore artificially large resulting in underestimation of both method and user failure rates.

Consider 100 women using a contraceptive pill for 12 months. Assume two pregnancies occur in 50 women with perfect use (method failures) and eight pregnancies occur in 50 women with imperfect use (user failures). Most would calculate a method failure rate of 2% and a user failure rate of 8%. By using the appropriate denominators, the true method contraceptive failure rate is 2/50 or 4% and the user contraceptive failure rate is 8/50 or 16%.

An alternative to the Pearl Index is life table analysis of the cumulative method failure rate. Life tables allow the calculation of contraceptive failure rates for each month of use and for any duration of exposure. Women can be classified based on the reason they stop contributing to contraceptive exposure time (accidental pregnancy, discontinuation, or loss to follow-up). Further data can be organized to reflect all failures within the first month of use, second month of use, etc. Finally, a standard error can be computed to reflect confidence in the cumulative failure rate estimate [5].

Beyond the challenges of calculating an accurate contraceptive failure rate, there are factors inherent to the research methods themselves that can lead to inaccurate reporting. First, all studies are at risk of selection bias since subjects entering a survey or trial may be inherently different than the "typical" woman. Second, we assume that subjects who are lost to follow-up will have the same risk of accidental pregnancy as those continuing in the study. However, a prior study found that women lost to follow-up had a higher accidental pregnancy rate than found in women continuing in the study, which may bias our results downward [6].

Recent studies on combined oral contraceptive pills have reported higher Pearl Indexes than older studies. This is not thought to be due to decreases in effectiveness but to changes in multiple study design factors including (1) more sensitive and frequent pregnancy testing and (2) decreased adherence among study participants [3].

- Up to 22% of pregnancies end in failure before diagnosed by the patient or physician [7]. However, in studies of contraceptive methods, frequent pregnancy testing with highly sensitive tests means many of these pregnancies, which would normally go unrecognized, are detected. Additionally, over time pregnancy tests have become more sensitive [8]. Early pregnancy tests were able to detect urine hCG at a sensitivity of 2000 IU/L and could not reliably identify pregnancies until 6 weeks after the last menstrual period. Today's ultrasensitive tests are able to detect hCG levels as low as 10 IU/L, allowing reliable diagnosis of pregnancy on the day of missing menses [9]. The evolution of pregnancy testing complicates the comparison of contraceptive failure rates between studies from different decades, as the pregnancy detection rate can vary dramatically based on the results [3].

Finally, the subjects themselves have a large influence on contraceptive failure rates. The fact that each woman will have different fecundability has already been mentioned. Beyond that, several other factors seem to influence contraceptive failure rates due to variability among subjects.

- First, prior use of hormonal contraceptives has been shown to increase contraceptive effectiveness, likely because prior users have more experience with correct use [10]. Their continuation of the method may indicate a satisfaction with the method, making them more motivated to use the method correctly. Indeed, the National Survey of Family Growth found women who were satisfied with contraceptive pills were more likely to use the pill correctly and miss fewer pills compared to women who were unsatisfied with the method.
- Second, prior pregnancy is associated with higher failure rates [10]. This may be a reflection of fecundability, as it demonstrates the woman is fertile.

- Third, obese women have been shown to be less compliant with pill use and, therefore, at a greater risk of contraceptive failure [11, 12].
- Fourth, race/ethnicity and geography play some role, as contraceptive failure rates are consistently higher in the United States than in Europe. Additionally, studies have found higher failure rates among Hispanic and Black women compared to White women [11, 13] though this may be confounded by socioeconomic status.
- Finally, socioeconomic status has consistently been associated with contraceptive effectiveness, with poorer women more likely to experience failures [11, 12, 14]. This may be due to a lack of access, lack of counseling or education, or other confounding factors not yet elucidated.

The fact that the individual characteristics of a contraceptive user so influences effectiveness emphasizes the importance of individualized contraceptive counseling, tailored to the patient.

Efficacy of Current Contraceptive Methods

The most comprehensive examination of contraceptive failure rates was done by Trussell [15] and Table 1.1 reflects his findings. The contraceptive failure rates were determined using national survey data and clinical trials data. They are subject to all the methodologic problems reviewed above. Some of the failure rates in the table are based on retrospective survey data and as a result are higher than failure rates from prospective studies discussed in the remainder of this chapter.

Efficacy of Current Emergency Contraceptive Methods

A recent Cochrane review found that the effectiveness of common oral emergency (within 120 hours of intercourse) contraceptive agents in order of most to least effective is mid-dose mifepristone (25–50 mg), low-dose mifepristone (<25 mg), ulipristal (30 mg once), levonorgestrel (both dosing regimens), and the Yuzpe method (ethinyl estradiol 100 μg/levonorgestrel 0.5 mg PO q12hrs × 2 doses) [16]. Some data indicate that oral emergency contraceptive methods may be less efficacious in overweight or obese women [17]. Although less convenient than oral regiments, the Copper IUD is the most effective emergency contraceptive and its efficacy is not affected by BMI. Mifepristone is not FDA approved for emergency contraception and as a result is not available in the United States for this indication.

Since studies comparing an emergency contraceptive treatment to a control group given placebo are not ethical, quantitative measures comparing observed to expected rates of pregnancy are not practical. Efficacy of emergency contraceptives

Table 1.1 Contraceptive efficacy and effectiveness by method

Method	% of women experiencing an unintended pregnancy within the first year of use		% of women continuing use at 1 year[a]
	Typical use[b]	Perfect use[c]	
No method[d]	85	85	
Spermicides[e]	28	18	42
Fertility awareness methods[f]	24		47
Standard days		5	
TwoDay		4	
Ovulation		3	
Symptothermal		0.4	
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Male condom	18	2	43
Diaphragm[g]	12	6	57
Combination pill and progestin-only pill	9	0.3	67
Combination patch	9	0.3	67
Combination ring	9	0.3	67
DMPA	6	0.2	56
IUD			
Copper	0.8	0.6	78
Levonorgestrel	0.2	0.2	80
Contraceptive implant	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Adapted from Trussell [15]

[a]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year

[b]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides and the diaphragm are taken from the 1995 NSFG corrected for underreporting of abortion; estimates for fertility awareness-based methods, withdrawal, male condom, the pill, and DMPA are taken from the 1995 and the 2002 NSFG corrected for underreporting of abortion

[c]Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), this refers to the percentage of couples who experience an accidental pregnancy during the first year if they do not stop using for any other reason

[d]The percentages becoming pregnant are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This number was lowered slightly to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether

[e]Includes foams, creams, gels, vaginal suppositories, and vaginal films

[f]Ovulation and TwoDay methods are based on evaluation of cervical mucus. The standard days method avoids intercourse on cycle days 8–19. The symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day

[g]Used with spermicide

Table 1.2 Emergency contraceptive failure rates by method

Method	Percent of women experiencing an unintended pregnancy with short-term follow-up
Copper IUD	0–0.14% [16, 18, 19]
Mid-dose mifepristone[a] (25–50 mg PO once)	1.2–2.1% [16]
Low-dose mifepristone[a] (<25 mg PO once)	1.5–1.7% [16, 20]
Ulipristal acetate (30 mg PO once)	1.3–1.9% [16, 21, 22]
Levonorgestrel[b] (1.5 mg PO once)	1.0–1.5% [16, 20]
Levonorgestrel[b] (0.75 mg PO q12hrs × 2 doses)	1.2–1.8% [16, 20]
Yuzpe method[c] (ethinyl estradiol 100 μg/ levonorgestrel 0.5 mg PO q12hrs × 2 doses)	2.0–2.9% [16, 23, 24]

[a]Not FDA approved for emergency contraception in the Unites States
[b]Maximum efficacy within 72 hours and reduced efficacy between 72 and 120 hours after unprotected intercourse
[c]Not recommended more than 72 hours after unprotected intercourse

can instead be quantified in terms of percentage of women who experience an unintended pregnancy as assessed during short-term follow-up such as 1 month after administration of the emergency contraceptive (Table 1.2).

No Method

Estimates of pregnancy rates among women not using contraception are based on studies following women who have discontinued contraception with the intention of conceiving. Among these women, pregnancy rates over 12 months range from 30% to 65% [25]. Women seeking pregnancy may behave differently than women attempting to avoid pregnancy, and so it is unlikely that woman trying to avoid pregnancy but not using a contraceptive method would have such a high 12 months' pregnancy rate. Indeed, Vaughan calculated a 12-month pregnancy rate of 46% among married women not seeking pregnancy and not using contraception [26]. This pregnancy rate may be underestimated as women not desiring pregnancy and electing not to use contraception may be subfertile or not engaging in regular intercourse. Others have estimated rates of pregnancy in patient populations not using contraception of approximately 85% in 1 year [15].

Female Sterilization

Data regarding failure rates of female sterilization are derived from the US Collaborative Review of Sterilization [27]. The overall failure rate of female sterilization was 0.6% at 1 year and 1.9% at 10 years for all methods combined. This would correspond to a Pearl Index of 0.6 over the first year or 0.19 over the first 10 years. Subsequent analysis of these data indicates that the failure rate with laparoscopic sterilization by fallopian tube electrocoagulation may be decreasing

as experience with laparoscopic surgery increases [28]. Hysteroscopic transcervical sterilization with the Essure device was approved by the FDA for use in the United States in 2002. However, because hysteroscopic sterilization is not effective until the microinserts have scarred the fallopian tubes closed (typically by 3 months after the procedure), decision analyses suggest that hysteroscopic transcervical sterilization may be less effective than traditional sterilization [29]. In 2018, sales of Essure in the United States were voluntarily discontinued by the manufacturer for business reasons. Any type of total bilateral salpingectomy is so effective that there are only rare case reports of spontaneous intrauterine pregnancy after the procedure [30, 31]. Failure rates for different methods of female sterilization are listed below in Table 1.3.

For sterilization procedures that remove or damage the fallopian tubes, there is no consideration of user error and the effectiveness is equal to efficacy. Tubal occlusion with Essure requires a 3-month postoperative confirmation test with a modified hysterosalpingogram or transvaginal ultrasound before it can be relied upon for contraception. For this reason, typical use failure rates include all women who have had Essure devices placed regardless of whether or not confirmation testing was performed and perfect use failure rates only include women who remained on an alternative form of contraception until a satisfactory Essure confirmation test was documented.

Male Sterilization

Most of the research on male sterilization uses postoperative azoospermia on semen analysis as the measure of success. There is limited research reporting rates of postoperative conception over time which is more clinically relevant and analogous

Table 1.3 Female sterilization failure rates by method

Method	Failure at 1 year (%)	Failure at 10 years (%)
Methods that remove or damage the fallopian tubes		
Bipolar coagulation	0.2	2.5
Unipolar coagulation	0.1	0.8
Silicone band	0.6	1.8
Spring clip	1.8	3.7
Interval partial salpingectomy	0.7	2.0
Postpartum partial salpingectomy	0.1	0.8
All above methods combined [27]	*0.6*	*1.9*
Total bilateral salpingectomy [30, 31]	Rare case reports only	
Method that occludes the fallopian tubes		
Hysteroscopic (Essure) [29]	5.7	9.6

to research on contraception and female sterilization. The efficacy of vasectomy was examined in the US Collaborative Review of Sterilization. Among 540 women whose husbands underwent vasectomy, conception occurred in 0.9% at 1 year and 1.3% at 5 years representing typical use rates of failure [32]. Half of the failures occurred within 3 months of vasectomy. A Cochrane review comparing rates of postoperative azoospermia after different vasectomy techniques found that intra vas devices were less effective than traditional vasectomy and that fascial interposition improved efficacy [33].

Intrauterine Devices (Paragard/Liletta/Mirena/Kyleena/Skyla)

There are five intrauterine devices (IUDs) available for use in the United States. One IUD contains copper as an active agent and four IUDs release levonorgestrel. Efficacy has been determined for these devices and a multitude of other intrauterine devices used worldwide. While it is preferable to examine first-year failure rates in order to appropriately compare contraceptives, many of the efficacy studies for IUDs report the failure rates over multiple years because the devices may be used for multiple years. Perfect use and typical use failure rates of IUDs are similar because user error such as unrecognized expulsion is rare. While most studies report failure rates as rates of conception, recent literature has begun to include Pearl Indexes more consistently. For ease of comparison, failure rates are listed in Table 1.4 for the five types of IUDs available in the United States at this time along with other relevant details.

Recent studies have found that copper IUDs such as the Paragard remain highly effective through 12 years of use and IUDs with 52 mg of levonorgestrel remain highly effective through 7 years [35, 42–44].

Table 1.4 Failure rates for IUDs available in the United States

Name	Active agent	Maximum duration recommended by manufacturer	One-year failure rate	Maximum duration failure rate
Paragard	Copper	10 years	0.3% [34]	1.3% [35]
Lilietta	Levonorgestrel 52 mg	6 years[a]	0.2% [36]	0.5% [36]
Mirena	Levonorgestrel 52 mg	5 years	0.0–0.6% [34, 37, 38]	0.5–1.1% [37, 39]
Kyleena	Levonorgestrel 19.5 mg	5 years	0.2% [40]	1.4% [41]
Skyla	Levonorgestrel 13.5 mg	3 years	0.4% [40]	1.0% [40]

[a]In 2019, the FDA approval for duration of pregnancy prevention with Liletta was increased from 5 to 6 years. The study cited for maximum duration failure rate for Liletta is based on the failure rate over 5 years

Etonogestrel Subdermal Implant (Nexplanon)

Nexplanon was introduced in 2010 as a replacement for the etonogestrel releasing subdermal implant Implanon. Compared to Implanon, Nexplanon has an improved insertion device, is radiopaque, and has the same maximum duration of use of 3 years. Most efficacy studies of the etonogestrel implant have reported no pregnancies during the study duration for a failure rate of 0% [45, 46]. Xu looked at use in normal weight, overweight, and obese women and found no pregnancies in the normal and overweight women, but a 3-year Pearl Index of 0.23 for obese women [47]. Darney performed a combined analysis of 11 clinical trials on Implanon and found a 1-year Pearl index of 0.24 and a 3-year Pearl Index of 0.34 [48]. The prescriber information for Nexplanon cites this study by Darney of Implanon use in the section discussing the rate of method failure [49]. Trussell estimates a failure rate of 0.05 per year for the implant [15]. Like sterilization and the IUD, the perfect and typical use failure rates are essentially identical, as there is no opportunity for user error and only minimal error due to insertion or placement issues.

Depot Medroxyprogesterone Acetate (Depo-Provera)

Depot medroxyprogesterone acetate (DMPA, trade name Depo-Provera) is available as an intramuscular injection or a subcutaneous injection. Both formulations provide contraceptive effectiveness for 15 weeks. The World Health Organization conducted two large multicenter trials that found IM DMPA failure rates in the first year of use of 0.1% in one trial and 0.7% in the other [50, 51]. A two-year study compared the efficacy of subcutaneous to intramuscular DMPA and found a Pearl Index of 0 for the SC administration route and 0.28 for the IM route [52].

Contraceptive Pills, Patches, and Rings

There have been dozens of studies assessing the efficacy and effectiveness of oral contraceptive pills. With perfect use, the one-year failure rate of the combination oral contraceptive pill is very low and has been estimated at 0.3% by Trussell [15]. The National Survey of Family Growth (NSFG) evaluates contraceptive use in a cross section of US women. The one-year failure rate reported by the NSFG of 9% is notably higher as it reflects typical use [14]. The best estimate of the theoretical efficacy of the progestin-only pill (also known as the minipill) is 99.0%, but failure rates with typical use may be somewhat higher than with the typical use of combination pills due to the very precise daily dosing schedule [53].

There is limited data on efficacy of generic oral contraceptive pills (OCPs) and antibiotic interference with OCP efficacy. Generic oral contraceptive pills must

show equivalent blood levels of active metabolites as compared to the brand product for FDA approval (additional efficacy testing is not required). Although generic pills are assumed to have the same efficacy as their branded products, differences in packaging and patient compliance may affect effectiveness [54]. Certain antibiotics are thought to decrease the effectiveness of oral contraceptive pills by increasing metabolism of the active agents in the liver, decreasing intestinal bacteria that help reabsorb metabolites secreted by the liver, or by other mechanisms. Rifampin has been shown to likely reduce OCP effectiveness and there is limited evidence that ampicillin, amoxicillin, metronidazole, and tetracycline may reduce OCP effectiveness. A second method of contraception should be recommended to women taking rifampin and can be offered to women taking ampicillin, amoxicillin, metronidazole, or tetracycline. While there have been case reports of pregnancies during concomitant use of OCPs with other antibiotics, data are limited and the use of a second method of contraception is generally thought to be unnecessary [55].

Previous reports of contraceptive efficacy have set the failure rates for the combination contraceptive patch and ring equal to those of the contraceptive pill. A multicenter study evaluating the efficacy of the vaginal ring reported a 1-year Pearl index of 0.77 with perfect use and 1.18 with typical use [56]. A 1-year randomized trial of 1030 subjects found comparable Pearl Indexes of 1.23 for the ring and 1.19 for OCPs in the intention to treat analysis [57]. One study compared the contraceptive patch to the contraceptive pill and found no statistical difference in either effectiveness or efficacy. The 1-year Pearl Indexes for the patch were 0.99 for perfect use and 1.24 for typical use. This compared to Pearl Indexes for OCPs of 1.25 for perfect use and 2.18 for typical use [58]. Typical use failure rates and Pearl Indexes may be lower for subjects participating in prospective research compared to subjects studied through retrospective surveys such as the National Survey of Family Growth [14]. There is a popular belief that the typical failure rates with the patch and the vaginal ring may be lower than typical failure rates with the pill because they require less frequent dosing by the user [59].

Condoms (Male and Female Versions)

Studies of condom efficacy often reflect typical use effectiveness compared to consistent use effectiveness rather than perfect use efficacy. This is due to the fact that perfect use requires consistent use at each coital act along with perfect placement and removal of the condom. Efficacy studies of condoms have also adjusted pregnancy rates taking into account use of emergency contraception which may decrease the number of reported failures.

Data from a 6-month study that combined results from two randomized controlled trials evaluating three male latex condom brands give a Pearl Index of 14 for typical use and 2 for consistent use. In this study 0.4% of condoms used for intercourse broke during intercourse and 1.1% of condoms slipped off during

intercourse or withdrawal [60]. In a randomized controlled trial, polyurethane condoms had a clinical failure rate (breakage or slippage during intercourse or withdrawal) of 8.5% compared to 1.6% for latex condoms. This 6-month study adjusted for emergency contraception and found a typical use Pearl Index of 9.6 for polyurethane condoms and 12.6 for latex condoms. The consistent typical use Peral Indexes were 4.8 for polyurethane condoms and 2.2 for latex condoms [61]. Other studies comparing polyurethane and latex condoms have also shown more frequent failure of polyurethane condoms, no significant difference in typical use pregnancy rates between the two types of condoms, and higher consistent use pregnancy rates with the polyurethane condoms than latex condoms [61–63]. Trussell reports a much higher typical use failure rate for the male condom of 17–18% over the first year based on NSFG population data [14, 15]. This retrospectively surveyed population may more accurately reflect the typical use in a general population than other studies based on participants that enroll in a prospective randomized controlled trial.

Data from one study give a 6-month Pearl Index for the female condom of 5.2 during perfect use in a US population [64]. This is higher than for the male condom; however, direct comparison is not possible due to lack of appropriately controlled prospective trials [65].

Female Barrier Methods (Diaphragm, Cervical Cap, and Contraceptive Sponge)

The female diaphragm, cervical cap, and contraceptive sponge are not as highly utilized today as they were in the past. It is relatively difficult to assess perfect use in studies of diaphragms, cervical caps, and sponges, as perfect use requires perfect placement with each coital act along with appropriate spermicide use and removal timing. Most studies measure consistent use (use with each coital act) failures. Analysis of nearly 3000 women demonstrates a first-year failure rate with perfect use of the diaphragm, cervical cap, and contraceptive sponge of 4–8%, 10–13%, and 11–12% respectively. Typical use first-year failure rates were significantly higher: 13–17% for the diaphragm, 18% for the cervical cap, and 17% for the contraceptive sponge [66].

Spermicides

Spermicides are marketed as gels, foam, film, or suppositories. In a randomized trial comparing these products, perfect use failure rates ranged from 5.1% to 15.7% and typical use failure rates ranged from 9.4% to 16.6% over the first six cycles of use [67, 68].

Lactational Amenorrhea Method

The lactational amenorrhea method (LAM) refers to the concept that amenorrhea associated with postpartum breastfeeding confers a contraceptive effect. Specifically, women who are (1) exclusively breastfeeding, (2) amenorrheic, and (3) less than 6 months postpartum have less than a 2% chance of conception over the course of the first 6 postpartum months (this is equivalent to a Pearl Index of less than 4). Data from a 6-month multicenter prospective study of the LAM give a Pearl Index of 2.2 for correct use [69]. Of the three criteria for use of the LAM, amenorrhea confers the greatest contraceptive effect. Thus, women who begin menstruating cannot rely on this method whereas women who are mostly but not exclusively breastfeeding but remain amenorrheic still experience low conception rates. However, lowering the frequency of breastfeeding will quicken the return of menses at which point the LAM can no longer be relied upon [70].

Fertility Awareness Methods (Also Known as Periodic Abstinence)

There are multiple protocols for detecting or predicting a woman's fertile days and avoiding intercourse on those days. Studies of these methods have involved intensive training of participants regarding the protocol and close follow-up to ensure participants understood how to use the method correctly. The TwoDay method relies only on detection of changes in cervical mucus. The Standard Days method requires avoiding intercourse from cycle day 8 through 19. In studies of these methods, the pregnancy rate after 13 menstrual cycles was 4–5% with perfect use and 12–14% with typical use [71, 72]. The symptothermal method combines cervical mucus changes and basal body temperature to determine the fertile window. This method performs best in clinical research where failure rates are reported as low as 1.8% in women utilizing typical use of this method over 13 cycles [73]. The ovulation method, which relies on periodic abstinence, has a failure rate of 3.1% during the first year with perfect use [74]. Periodic abstinence methods can be very effective when used perfectly, but very ineffective when used in the general population where motivation may be less or the opportunity to educate patients about the method is limited.

Withdrawal

Withdrawal or coitus interruptus is frequently used as a contraceptive method, but it is not frequently discussed with patients during contraceptive counseling, nor is it well studied. A 47-month retrospective study found that 21% of subjects that used

the withdrawal method had an unintended pregnancy during the study timeframe [75]. Efficacy rates for perfect use are generally a guess based on some evidence that there are few motile sperm in pre-ejaculatory fluid. Typical use failure rates are also estimated using NSFG data and are notably high [14, 15].

Simultaneous Use of Multiple Methods

There is almost no data on failure rates of simultaneous use of two or more methods of contraception. Models suggest that simultaneous use of two moderately efficacious methods can be highly efficacious with consistent use [76]. Use of condoms to decrease the risk of STD transmission along with a more effective method of contraception is a natural pairing.

Contraceptive Counseling

Some contraceptive options have noncontraceptive benefits and medical indications that are important to consider during patient counseling. The Mirena IUD is indicated for abnormal uterine bleeding, OCPs can be used to regulate menstrual patterns, and condoms decrease the transmission of sexually transmitted diseases. The copper IUD can be used for both emergency contraception and continued long-acting reversible contraception. Bilateral salpingectomy has been shown to reduce the risk of ovarian cancer (which is thought to sometimes originate from the fallopian tubes).

While there are challenges in determining exactly how well a contraceptive method will work for any given women, the effectiveness of each contraceptive method is an important part of contraceptive counseling. On the whole, women should be given personalized and accurate information to guide them in identifying the contraceptive method that best fits their lifestyle, preferences, and goals. Sadly, surveys show that many women are given inaccurate, outdated, or biased information during contraceptive counseling [77–79].

In a recent survey of 400 women, the following were identified as the most important questions that women wanted answered during their counseling experience with a healthcare provider [80]:

1. Is it safe?
2. How does it work? (mechanism of action)
3. How do I use it?
4. What side effects does it cause?
5. How effective is it with perfect and typical use?
6. How frequently do I have to use it?
7. When does it begin working to prevent pregnancy?

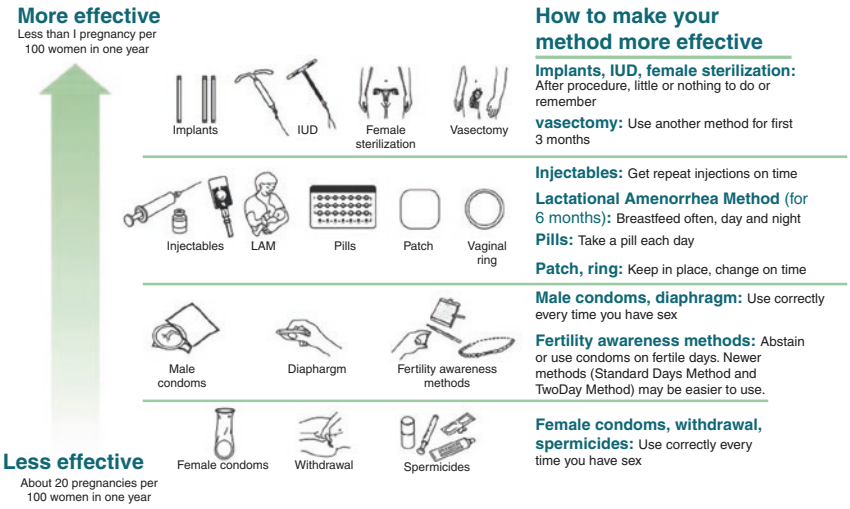

Fig. 1.1 Comparing effectiveness of family planning methods. (Used with permission for Ref. [84])

Despite the importance of contraceptive counseling, little research has been done to elucidate effective strategies that actually influence behavior positively. We do know that despite accurate counseling, women frequently underestimate the efficacy and effectiveness of long-acting reversible (LARC) methods and overestimate the efficacy and effectiveness of the oral contraceptive pill, patch, ring, condoms, and depot medroxyprogesterone acetate (Depo-Provera) [81]. There is evidence to suggest that charts grouping contraceptives by efficacy (Fig. 1.1) are easier for patients to understand than tables that list numeric failure rates [82]. However, studies evaluating multiple counseling sessions, inclusion of partners, or standard scripts found no improvement in subsequent contraceptive behaviors [83].

Qualitative contraceptive research has demonstrated repeatedly that the physician is but one influence when it comes to decision making regarding contraception. Many women, especially young women, express significant embarrassment in talking about contraception with a provider. This may be in part linked to the fact that many women have very little baseline knowledge about contraception [85]. A qualitative analysis suggests that many women equate contraception with the contraceptive pill, as the pill has been their primary experience with contraception [86]. Finally, women are highly influenced by family and friends [78, 85–87].

When we consider these factors, it is easy to conclude that contraceptive counseling should be routinely provided without patient prompting and efforts made to decrease any element of embarrassment that some women may have with this topic. Informational brochures categorizing methods by most to least efficacious in a pictorial form should be readily available to all women.

Perhaps most importantly, the discussion about contraception should include an exploration of attitudes about contraception held by the patient's friends, family, and partner and address the issues most important to the patient such as the following:

- Having a period versus not having one
- Ease of use
- Fertility plans
- Fear of side effects

However, recognizing that our interactions with patients are limited by time constraints, it is important to consider contraceptive counseling as an ongoing dialogue to be addressed again and again in subsequent visits. When time constraints force counseling to be limited, counseling should focus on

- Most effective methods first
- Methods in which efficacy is equal to effectiveness (little room for user error)
- Methods a woman will actually use

Conclusion

There are multiple contraceptive options available to women. The ways in which we calculate the effectiveness and efficacy of these methods are imperfect. Contraceptive methods that are long acting and require less frequent effort on the part of the user are more effective than those that require daily use, use with coitus, or are short acting. The patient's ability to correctly and consistently use a method is extremely important in determining effectiveness of a contraceptive. Total bilateral salpingectomy is the most efficacious method of contraception with a failure rate so low that only a few case reports of postoperative conception have been documented. The failure rates of the subdermal implant and IUDs are similar to methods of female surgical sterilization (other than total bilateral salpingectomy). While there are many highly efficacious reversible methods of contraception available, no reversible method has a 0% failure rate.

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Chapter 2
Combination Oral Contraceptive Pills

Luu D. Ireland and Rebecca H. Allen

Introduction

Overview

Combination oral contraceptive pills (COCs) have been available in the United States for over 50 years and are the most common form of contraception used by US women. Up to 82% of women who have ever been sexually active have used COCs and 19.4% of women of reproductive age who use contraception report current COC use. Combined oral contraceptive pills have two hormonal components, an estrogen and a progestin. The first pill, Enovid-10, was introduced in 1960 and contained 150 μg mestranol and 9.85 mg norethynodrel, doses significantly higher than those in currently available COCs.

Early COCs contained mestranol, a biologically inactive pro-drug, which is demethylated in the liver during first-pass metabolism to ethinyl estradiol (EE). The conversion efficiency of this process is 70% (meaning that 50 μg mestranol is equivalent to 35 μg EE). During the next several decades, EE gradually replaced mestranol in COC formulations.

Because orally administered estrogen increases the risk of both arterial and venous thrombosis in a dose-dependent manner, an effort was made to reduce the dose of EE in COC formulations. In the United States, the estrogen dose was initially lowered from 150 μg of mestranol to 50 μg. Further reductions over time have

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resulted in a large number of products with 35, 30, 25, and 20 μg of EE and one product containing only 10 μg. The data regarding safety of 20 μg versus 25, 30, or 35 μg EE COCs are not strong enough to endorse higher safety for pills containing 20 μg or less. Recently, COC formulations containing estradiol (estradiol valerate (E2V) and 17-beta estradiol) were developed with the theoretical benefit that using a nonsynthetic estrogen might decrease the thrombotic risks and metabolic effects associated with EE formulations.

The evolution of the COC also involved a reduction of progestin doses and development of newer progestins that are more potent and have longer half-lives than norethynodrel. Modern COCs contain progestins derived from progesterone, testosterone, or spironolactone (Table 2.1). All progestins, even those derived from testosterone, have a low degree of androgenicity, especially when used clinically by humans in combination with estrogen. The more recently introduced gonane progestins (norgestimate, desogestrel, and gestodene) are also derivatives of testosterone, but they have less androgenic activity in vitro than the older progestins. Drospirenone, a progestin structurally related to spironolactone, exhibits progestogenic, antimineralocorticoid, and antiandrogenic activities. The newest progestins, nomegestrol acetate and dienogest, primarily have progestogenic activities. Dienogest also has antiandrogenic activity.

Product Description

Many preparations of COCs exist, varying by hormone types, dosages, and duration of hormone-free intervals. COCs with monthly cycling are typically packaged in 28-pill packs and available in monophasic or multiphasic preparations. Monophasic formulations contain the same amount of estrogen and progestin in each active pill in the pack. Typically, the packs contain 21 or 24 identical active pills with the remainder of the 28-pill package being placebo pills. Withdrawal bleeding will typically occur during the placebo hormone-free interval. COCs containing 24 active pills and 4 placebo pills (24/4) may be associated with increased efficacy given that there is decreased risk of folliculogenesis during the hormone-free interval compared to 7 days. These formulations have also been associated with decreased symptoms associated with hormone withdrawal (e.g., mood symptoms, headache, and pelvic pain) and improved bleeding control.

Multiphasic formulations contain pills with different combinations of estrogen and progestin in the same pack. The goal of using a variety of different dosages in each pill pack is to minimize hormonal exposure while providing reliable ovulation suppression. Biphasic, triphasic, and quadriphasic formulations are available. Importantly, no studies have ever shown a clinically relevant benefit of multiphasic preparations over monophasic preparations.

Extended-cycle COC formulations are available for patients who desire longer than 28-day cycles. Contraceptive efficacy, safety, and patient satisfaction are

Table 2.1 Progestins used in COCs

	Progesterone		Testosterone		Spironolactone
Parent component	19-Norprogesterone	17α-Hydroxy-progestrone	19-Nortestosterone		17α-Spironolactone
Class name	Norpregnanes	Pregnanes	Estranes	Gonanes	Spironolactone
Product name	Nomegestrol acetate		Norethindrone	Norgestrel/levonorgestrel	Drospirenone
			Norethindrone acetate	Norgestimate	
			Ethynodiol diacetate	Desogestrel	
			Norethynodrel	Gestodene	
		Dienogest[a]			

[a]Dienogest is a hybrid progestin

similar for cyclic and extended-cycle regimens. These formulations offer the noncontraceptive benefit of fewer bleeding episodes per year for lifestyle preferences and can also be used to alleviate dysmenorrhea and endometriosis pain. Although there are dedicated products providing three continuous months of hormonal pills, most monophasic preparations can also be used safely and effectively in a continuous manner simply by skipping the placebo pills.

Mechanism of Action

The contraceptive effect of COCs is provided primarily by the progestin component. The primary mechanism of action is inhibition of the midcycle luteinizing hormone surge resulting in ovulation suppression. The estrogen component also contributes to contraceptive action by suppressing ovarian folliculogenesis through suppression of pituitary follicle-stimulating hormone secretion. A secondary mechanism of action, inhibiting sperm from ascending to the upper genital tract through thickening of the cervical mucus and endometrial atrophy, becomes more important for women using very low-dose preparations or when pills are not taken on time.

The magnitude of hypothalamic–pituitary suppression is unrelated to the age of the woman or the duration of steroid use but is related to the potency of the progestin and estrogen in the formulation. After discontinuing current low-dose formulations, return to ovulation is usually rapid. However, because the suppression is so quickly reversible, there is less room for error when using current low-dose ($\leq$35 μg) COCs. Extending the pill-free interval for more than 7 days may result in breakthrough ovulation and pregnancy. Women should be advised that the most important pills to remember to take are the first ones of each cycle.

Clinical Effectiveness

COCs are considered second-tier contraceptives due to their first-year typical use failure rate of 7%. Although contraceptive failure rates are lower with consistent and correct use and in experienced consumers, all individuals are real-life users. No significant differences in clinical effectiveness have been demonstrated for the various COCs currently available. The risk of contraception failure is highest if pills are missed at the beginning of the cycle.

Barriers to successful COC use exist at multiple levels. Requiring patients to refill their prescriptions monthly is associated with lower continuation rates than when multiple packs are provided. Pregnancy ambivalence is an example of a patient-level barrier. Individuals who do not feel strongly about avoiding a pregnancy may be less motivated to adhere to a daily pill schedule. It is important to note that COC users have high rates of discontinuation. Studies report that at 6 months

of use, 28% of women have stopped their pill, and by 12 months, this number reaches nearly 50%. Vulnerable populations, such as adolescents, patients of color, or those facing financial hardship, are more likely to report discontinuation of COCs. Many patients discontinue COCs without consulting their providers. For this reason, it is important to discuss use of other methods (such as condoms) in case discontinuation occurs before patients return for a follow-up. Individuals choosing COCs should also routinely be informed about emergency contraception and provided a prescription when necessary to ensure access.

Despite the small increase in risk of venothromboembolism, COCs have an excellent safety profile. For most healthy, nonsmoking sexually active patients, the risk of using any contraceptive method is safer than using no method. The maternal mortality ratio in the United States has steadily increased over the last two decades, with 17.2 pregnancy-related deaths per 100,000 live births reported in 2015. Since half of pregnancies in this country are unintended, preventing those pregnancies through contraceptive use could substantially reduce maternal deaths. Additionally, COCs reduce the risk of ectopic pregnancy, the leading cause of pregnancy-related deaths in the first trimester, by 90%.

Contraceptive Benefits

For many individuals, COCs provide an effective method of pregnancy prevention, which allows users the autonomy to decide when to initiate or stop contraceptive use. Unlike progestin-only contraceptive methods, COCs provide a predictable bleeding pattern. Upon cessation of the method, return to fertility is quick, with an 87% rate of conception in the first 12 months following COC use.

Noncontraceptive Health Benefits

In addition to contraceptive protection, COCs provide a wide range of other health benefits. The vast majority of these benefits are not FDA-approved indications for COC use, but the clinician and users may want to consider them in their overall assessment.

Noncontraceptive Health Benefits of COCs

- Reduction in the amount of monthly blood loss resulting from hormonal action on the endometrium.
  - In an ovulatory cycle, the mean blood loss is about 35 mL, compared with 20 mL in COC users.
  - COCs are often an effective treatment for heavy menstrual bleeding.

  - All COC formulations are associated with improvements in menstrual bleeding, though only Natazia® (estradiol valerate + dienogest) has FDA approval for this indication.
  - Less iron-deficiency anemia.
- Fewer menstrual irregularities; COCs are designed to produce regular withdrawal bleeding.
- Decreased lifetime risk of endometrial cancer.
  - COC use for 1 year reduces the risk by 40% and by 80% after 10 years of use.
  - Protection lasts for up to 20 years.
- Decreased lifetime risk of ovarian cancer.
  - Risk is reduced by >40% after ever-use and by 80% after 10 years of use.
  - Protection lasts for up to 20 years.
- Protection includes women with a BRCA mutation or strong family history of ovarian cancer.
- Lower risk of benign breast disease, including cysts, fibrocystic changes, and fibroadenomas.
- Less dysmenorrhea.
- Lower incidence of symptomatic endometriosis.
- Less premenstrual syndrome symptoms including bloating, pelvic pain, cramping, and mastalgia.
  - Yaz® is FDA approved for treatment of premenstrual dysphoric disorder.
- Lower rate of functional ovarian cysts, although follicular cyst formation may not be eliminated with low-dose COCs.
- Lower incidence of androgen-excess conditions.
  - Reduction in acne lesions and hirsutism.
  - All formulations are associated with improvements in mild to moderate acne; only Ortho Tri-Cyclen®, Estrostep®, and Yaz® have FDA approval for treatment.
- Less mittelschmerz (midcycle ovulation pain).
- Reduction in hot flashes and other perimenopausal symptoms.

Patient Selection

Patient preference should always guide decisions regarding contraceptive choice. Individuals seeking to prevent pregnancy for 1 year or longer may be better suited for a long-acting reversible contraceptive (LARC) method, such as intrauterine devices or the subdermal contraceptive implant, rather than a COC or other

short-acting options. Similarly, those who do not feel they can realistically adhere to a daily pill regimen should consider other options. The needs of special populations should also be taken into account. Adolescents, for instance, have a significantly higher risk of unintended pregnancy when using short-acting methods compared to adults.

A thorough review of the patient's medical history (including medications) is necessary to identify risk factors for venous thromboembolic disease or contraindications to the hormones in COCs as discussed below.

According to the CDC's Selected Practice Recommendations (SPR) for Contraceptive Use, blood pressure evaluation is the only examination required to determine eligibility for COC use. No pelvic examination, sexually transmitted infection (STI) testing, or Pap tests are required for COC initiation or use. Although other factors in the patient's history and personal preferences will also influence their choice of contraception, eligibility for COC use is limited to taking a history and evaluating blood pressure.

Contraindications to Use

It is important for healthcare providers to have a full and accurate understanding of *real* contraindications to COC use. For example, while many providers express hesitation to prescribe COCs to women with a family history of breast cancer, it is important to note that COC use in such women does not alter their own risk of breast cancer. The CDC U.S. Medical Eligibility Criteria (MEC) for Contraceptive Use is a complete resource to help providers understand evidence-based indications and contraindications. Based on a systematic review of available evidence regarding the safety of contraceptives among women with various medical conditions, recommendations for contraceptive use are classified under one of four categories. Category 1 denotes a condition for which there is no restriction for the use of the contraceptive method. A condition for which the advantages of using the method generally outweigh the theoretical or proven risks is category 2. When the theoretical or proven risks of a condition outweigh the advantages of using the method, it is classified as category 3. Finally, a condition that represents an unacceptable health risk if the contraceptive method is used is categorized as 4. Relative and absolute contraindications (conditions under US MEC categories 3 and 4) are summarized below. Additionally, certain medications interact with COCs in a negative way to potentially decrease the ability of systemically administered hormones to prevent pregnancy (Table 2.2).

Table 2.2 Combined oral contraceptives and other drug interactions

Drugs that may decrease the effectiveness of COCs, result in breakthrough spotting, or interfere with the drug's blood level or therapeutic action
Medications that may interfere with COC action:
Over-the-counter medications: St. John's wort may reduce effectiveness of COCs
Anticonvulsants: Many anticonvulsants induce cytochrome P-450 activity and can have significant effects on COC hormone levels. The following are MEC Category 3:
Barbiturates
Carbamazepine
Phenobarbital
Phenytoin
Primidone
Topiramate
Oxcarbazepine
Antiretrovirals (ART): Certain antiretrovirals may adversely affect COC effectiveness. The following are considered MEC Category 2:
Efavirenz (NNRTI)
Ritonavir (PI)
Ritonavir-boosted protease inhibitors
Atazanavir (PI)
Fosamprenavir (PI) MEC Category 3
Nelfinavir (PI)
Anti-TB medications: May adversely affect COC effectiveness
Rifampin or rifabutin MEC Category 3
Broad-spectrum antibiotics: Most broad-spectrum antibiotics do not affect the contraceptive effectiveness of COCs and are considered MEC Category 1
Oral contraceptives may interfere with the action of certain medications
Lamotrigine: COCs decrease the levels of lamotrigine in women taking lamotrigine as monotherapy MEC Category 3
Thyroid medication: Increases in sex hormone-binding globulin may impact thyroid function testing results and may alter required dosage of medication *Potassium-sparing drugs*: Women who use ACE inhibitors, potassium-sparing diuretics, heparin, angiotensin-II receptor inhibitors, aldosterone antagonists, or daily NSAIDs may be monitored for potassium during the first months of use of DRSP-containing COCs. Multiple studies demonstrate safety of DRSP-containing pills for patients on these medications
COC combined oral contraceptive, *ACE* angiotensin-converting enzyme, *NSAID* nonsteroidal anti-inflammatory drug, *DRSP* drospirenone, *NNRTI* non-nuceloside reverse transcriptase inhibitors, *PI* protease inhibitor

Absolute Contraindications to COC Use (US MEC 4)

- Cigarette smoking of more than 15 cigarettes per day in women 35 years or older
- Multiple risk factors for arterial cardiovascular disease (older age, smoking, diabetes, hypertension)
- Uncontrolled hypertension
- Elevated blood pressure levels (Systolic ≥160 mmHg or diastolic ≥100 mmHg)
- Migraine at any age with localizing neurological signs, including aura/scotomata

- Postpartum <21 days
- Personal history of deep venous thrombosis (DVT) or pulmonary embolism (PE) with higher risk of recurrence
- Acute DVT/PE
- Major surgery with prolonged immobilization
- Known thrombogenic mutations (factor V Leiden, protein S, protein C, prothrombin, and antithrombin deficiency)
- Complicated valvular heart disease with pulmonary hypertension, subacute bacterial endocarditis, or atrial fibrillation
- History of peripartum cardiomyopathy (any severity) within the last 6 months
- Any history of peripartum cardiomyopathy with moderately or severely impaired cardiac function (New York Heart Association Functional Class III or IV)
- Systemic lupus erythematosus (SLE) with positive (or unknown) antiphospholipid antibodies
- Breast cancer (current)
- Known or suspected vascular disease
- Cerebrovascular or coronary artery disease, history of stroke
- Ischemic heart disease (current or past)
- Diabetes with vascular disease including retinopathy or nephropathy
- Diabetes for more than 20 years
- Active viral hepatitis, acute, or flare (only for initiation; discontinuation of current COC use not indicated for a new diagnosis)
- Severe (decompensated) cirrhosis

- Benign hepatocellular adenoma or malignant hepatoma
- History of complicated solid organ transplantation with graft failure (acute or chronic), rejection, cardiac allograft vasculopathy
- Hypersensitivity to any component of the pill

Risks Generally Outweigh Benefits (US MEC 3)

- Postpartum 21–30 days if primarily breastfeeding or postpartum 21–42 days with risk factors for venous thromboembolism (e.g., age ≥35 years, previous venous thromboembolism (VTE), thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, BMI ≥30 kg/m^2, postpartum hemorrhage, postcesarean delivery, preeclampsia, or smoking)
- Cigarette smoking of less than 15 cigarettes per day in women 35 years or older
- History of malabsorptive bariatric procedures (Roux-en-Y gastric bypass, biliopancreatic diversion)
- History of adequately controlled hypertension or mildly elevated blood pressure levels (systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg)
- Personal history of DVT/PE, lower risk for recurrence (no risk factors)
- Acute or history of superficial venous thrombosis
- History of peripartum cardiomyopathy more than 6 months previously, with normal or mildly impaired cardiac function (New York Heart Association Functional Class I or II)
- Previous breast cancer but no evidence of current disease for 5 years
- Inflammatory bowel disease (IBD) with increased risk of venous thromboembolism (active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, or fluid depletion)
- History of COC-related cholestasis or current symptomatic gall bladder disease treated medically
- Multiple sclerosis with prolonged immobility
- Certain antiretrovirals, anticonvulsants, or antibiotics (Table 2.2)

Patient Educational Points

Counseling Tips

Choosing a contraceptive method involves balancing the risks and benefits of each method in the context of a patient's individual preferences. Ideally, a potential user should choose the most effective method she thinks she would be able to use consistently and correctly. The best counseling strategy to accomplish this goal is unclear, but individuals generally want to know the following characteristics of a contraceptive method before deciding what will work for them: safety, effectiveness,

availability, convenience, risk of side effects, cost, and noncontraceptive benefits, among others. An individual's personal considerations will vary so it is important to ask each individual what they value in their contraceptive method and address their concerns directly and honestly. Some patients may welcome provider participation in the decision-making process in a way that emphasizes their values and preferences. Counseling should include practical information on how to use COCs and anticipatory guidance regarding side effects.

Discussing Advantages and Disadvantages of COCs

Advantages of COCs

- Moderately effective if taken correctly.
- Relatively easy to use and not coital-dependent.
- Rapidly reversible: most women become pregnant within 4–6 months after discontinuing use.
- Safe: healthy, nonsmoking, normotensive women can use COCs safely throughout their reproductive years.
- COCs are associated with a long list of contraceptive and noncontraceptive health benefits, including:
  - Decreased menstrual blood loss, decreased menstrual cramping, control of bleeding patterns
  - Improvements in androgen-related problems (such as acne or hirsutism) and premenstrual syndrome
  - Decreased risk of ovarian cysts and benign breast disease
  - Decreased lifetime risk of ovarian and endometrial cancer

Disadvantages of COCs

- Less effective for contraception than long-acting reversible contraceptives such as IUDs and contraceptive implants.
- Require daily use.
- Although COCs are used to prevent pregnancy when having sex, COCs do not provide protection from STIs or HIV transmission that can occur during sex; a male latex condom is the best method to use to prevent infection.
- Cost is a major issue for women. A one-month supply of COCs may be as high as $80 depending on type of pill, insurance coverage, and copay required.
- The number of COC packs dispensed by pharmacies can be restricted such that frequent visits to the pharmacy are required for perfect COC use.
- Privacy can be an issue for women who have partners or parents who may not be supportive of COC use.
- Side effects including breast tenderness, nausea, headache, mood changes, bloating, skin changes, and unscheduled vaginal spotting or bleeding.

- Rare, serious risks of COC use including:
  - Venous thromboembolism (venous thrombosis and pulmonary embolism)—Although COCs increase the risk of venous thromboembolism twofold to fourfold, the risk is half compared with the risk associated with pregnancy.
  - Hypertension—Elevated blood pressure occurs in 41.5 cases per 10,000 COC users.

Patient Screening

A thorough review of the patient's medication list and medical history is necessary to identify contraindications to hormonal contraception. According to the CDC's Selected Practice Recommendations for Contraceptive Use, blood pressure evaluation is the only screening examination required to determine eligibility for COC use.

Timing of Initiation

New Start

COCs can be initiated at any time if it is reasonably certain the patient is not pregnant. Over the years, providers have counseled patients in various ways to start using a COC, including waiting until the first day of their next menses or waiting until the first Sunday after their next menses. Both of these methods require waiting to start their desired method, potentially delaying the onset of contraceptive protection or noncontraceptive benefit. The "Sunday start" method requires an additional 7 days of using a backup method (or abstinence) once the pill is started, although it does have the advantage of avoiding withdrawal bleeding on the weekends with packages containing 21 active pills (desired by some users).

> In the early 2000s, "quick start" of contraceptive methods became more popular as an evidence-based manner of starting contraception. With quick start, contraceptives are initiated as soon as the same day of the visit with the healthcare provider. This method has the potential to minimize the risk of unintended pregnancy and should be recommended to patients.

Quick start of COCs requires a backup method (or abstinence) for 7 days unless COCs are initiated within the first 5 days of menses. "Quick start" users may switch to Sunday start with the next cycle if withdrawal bleeding on the weekend is bothersome.

Switching from Other Method

Individuals who are switching from another contraceptive method should start COC use the same day they discontinue their former method. If it has been more than 5 days from their last scheduled bleed, they should use backup contraception for the first 7 days of COC use. The exception is in those patients transitioning from IUD to COC use. If an individual has had sex without a barrier method in the 5 days prior to IUD removal, there is potential for pregnancy to occur from residual sperm in the genital tract. In this case, the patient has several options. One option is to start COCs and return for IUD removal in 7 days. Another option is to take emergency contraception and start COC use immediately if levonorgestrel emergency contraception is used or 5 days later if ulipristal acetate is used.

Postpartum or Postabortal

The postpartum period is a hypercoaguable state. The risk of venous thromboembolism is highest at the time of delivery and decreases sharply throughout the first 21 days postpartum. Because of this, it is advised that healthy postpartum patients without risk factors delay the initiation of estrogen-containing COCs until 21 days postpartum. Individuals with risk factors for VTE (age ≥35 years, prior history of VTE, immobility, transfusion at time of delivery or postpartum, obesity, history of recent postpartum hemorrhage, cesarean delivery, or smoking) should delay COC initiation until 42 days postpartum.

The concern for the impact of COC use on lactation was largely based on older studies using high-dose COC regimens, typically greater than 35 μg EE per day. However, as more reassuring data have emerged, the US MEC concluded that the benefits of COC use outweigh the theoretical risks as early as 30 days postpartum in healthy individuals without risk factors for VTE.

Patients can initiate COC use at any time after first or second trimester abortion or pregnancy loss. If conception is not desired, COC use should be initiated immediately to prevent unintended pregnancy.

Dispensing the Method

Factors to take into consideration when selecting a COC include a patient's past experience with COCs, patient preferences, clinical characteristics, insurance coverage, and cost. Patients traditionally initiate COC use after receipt of a prescription by their healthcare provider. However, lack of time, transportation, insurance coverage, or other financial limitations can compromise an individual's access to a healthcare provider. Several states have taken measures to improve contraceptive access. As of February 2019, nine states (CA, CO, HI, ID, MD, NM, OR, TN, and WA) and the District of Columbia permit pharmacists to prescribe COCs directly to patients.

The need for regular pharmacy visits to refill prescriptions presents another challenge to COC access. In fact, patients who receive a 1- to 3-month supply of COCs

are 30% more likely to have an unintended pregnancy compared to those who received a 12-month supply. Although US-based insurance companies will honor a year's worth of refills, many patients have insurance plans that only allow them to receive one pack of pills each month, and they must return monthly to the pharmacy to obtain their medication. As a result, 16 states (CA, CO, CT, ED, HI, IL, ME, MA, NV, NH, NY, OR, RI, VT, VA, and WA) plus the District of Columbia have passed laws requiring insurers to provide coverage for a 12-month supply of contraceptives. Outside of these states, insurance plans may permit a 3-month supply through mail-order pharmacies. Whenever possible, healthcare providers should prescribe patients with longer lasting supplies of COCs. No follow-up is required after COC initiation.

Managing Problems

When initiating COC use, healthcare providers should provide anticipatory guidance regarding expected side effects, as well as strategies for maximizing contraception in the inevitable event of missed pill doses. These strategies are outlined below.

Side Effects

- Irregular bleeding or spotting may be expected for 3–4 months after starting a new COC.
- Minor side effects, such as breast tenderness, nausea, and headache, are likely to decrease after several cycles.
  - Side effects may be minimized if the pill is taken the same time every day or if taken with a meal.
  - Side effects may be less bothersome if pill is taken at bedtime.
- COCs provide no protection from sexually transmitted infection (STI), and users at risk for STI exposure should be counseled on concomitant condom use.
- Missing pills during first week of pill pack.
  - Missing one pill in first week of a new cycle: take tablet as soon as remembered and the next one at the correct time; use barrier backup method for 7 days (consider emergency contraception if intercourse occurred within the past 5 days).
  - Missing two or more pills: take two pills as soon as possible and then two more the following day; use backup protection until the next pill pack (consider emergency contraception if intercourse occurred within past 5 days).

- Missing pills after first week of pill pack (or a non-placebo pill during fourth week of pill pack).
  - Missing one pill: take two pills as soon as possible; no backup needed.
  - Missing two pills (2 days in a row): take two pills as soon as possible and then two more the following day. Use backup protection until the next pill pack.
  - Missing more than two pills: discard current pack and begin a new cycle, use a backup method until 7 days into the next cycle (consider emergency contraception if intercourse occurred within the past 5 days).
- Missing placebo pills: discard pill and take next one on time (placebo pills do not need to be taken if the patient knows when to start her next package).
- Light or missing periods.
  - A short or scanty period (a drop of blood) counts as withdrawal bleeding as long as it occurs during the pill-free/placebo pill interval.
  - If one period is missed and no pills in that cycle have been missed, pregnancy is unlikely.
  - If any pills were missed in that cycle or if there is concern, a pregnancy test is advised.
  - If no withdrawal bleeding occurs for two cycles, a pregnancy test should be done and if negative can consider switching to a COC with a different progestin or slightly more estrogen.

Warning Signs

Although serious complications from COCs are very rare, patients should also be instructed on warning signs of serious adverse events. A useful mnemonic is *ACHES*. Patients should stop their pills and seek immediate evaluation if they have severe *A*bdominal pain (could be a sign of mesenteric or pelvic vein thrombosis or ectopic pregnancy), *C*hest pain (could indicate pulmonary embolus or myocardial infarction), *H*eadaches (could be a sign of a stroke), *E*ye problems (could indicate stroke or retinal vein thrombosis), or *S*evere leg pain (could indicate a deep venous thrombosis). If COCs are stopped due to concern for an adverse event, it is important that patients seek care immediately and use another method of contraception, such as condoms, in the interim.

Drug Interactions

Several classes of medications will result in unfavorable drug interactions when used in combination with COC use. It is important for providers to be familiar with these potential interactions (Table 2.2).

Summary

COCs were an important advancement for women in 1960 when the only other widely available female-controlled contraceptive was the diaphragm. It is a moderately effective method compared to other contraceptive options in use today. COCs have many noncontraceptive benefits and may be used by some women to improve menstrual patterns, lessen dysmenorrhea, decrease PMS, or ameliorate acne. Low-dose COCs (formulations containing <50 mcg EE) are a safe and reliable contraceptive option for the vast majority of individuals. For healthy, nonsmoking patients, COCs may be continued until the age of menopause.

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Chapter 3
Progestin-Only Oral Contraceptives

Benjamin P. Brown and Rebecca H. Allen

Introduction

Progestin-only pills (POPs) are often referred to as "mini-pills" as they contain about 25–75% of the progestin dose contained in combination oral contraceptives (COCs), depending on the type, and no estrogen. Their typical-use effectiveness has been shown to be slightly less than COCs, most likely due to a more limited duration of effect, inconsistent ovulation suppression, and difficulties with adherence. POPs are associated with more breakthrough bleeding than COCs but fewer serious adverse events. Although not as well studied, POPs are thought to have many of the same noncontraceptive health benefits as COCs.

Reported failure rates for POPs vary significantly. This variation is most likely due to differences in population adherence, the difference in ovulation suppression seen with various progestin components, and their high use in populations of lower fecundity (individuals over 40 years old or breast-feeding patients). Population data are largely unable to distinguish the effectiveness of POPs from COCs, so likely the best approximation of the typical-use POP failure rate is near or somewhat over 10%. A 2010 Cochrane review concluded that data were insufficient for a direct comparison between POPs and COCs, or between different POP formulations.

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To a limited degree, POPs disrupt the mid-cycle peak of luteinizing hormone, thereby suppressing ovulation. However, the extent of ovulation suppression varies depending on the type of progestin component and patient adherence. POPs have several other mechanisms that prevent pregnancy including the following:

- Cervical mucus thickening to prevent sperm penetration. This effect is time limited and appears to wane quickly after 24 hours; thus, a POP is considered missed if it has been >3 hours since the time at which it should have been taken.
- Reducing cilia motion in the fallopian tube, thus inhibiting ova and sperm transport.
- Reducing the size and number of endometrial glands and changing progesterone receptors in the endometrium, which makes it appear more inactive. It is unknown if this impacts sperm transport or implantation.

Contraceptive Benefits and Noncontraceptive Benefits

Contraceptive Benefits

Good option when estrogen is contraindicated: POPs are not linked to many of the rare but serious side effects of COCs, such as venous thromboembolic events.

- Simple regimen because the user takes the same pill every day with no break.
- Quick return of fertility upon discontinuation.
- No effect on bone density.

Noncontraceptive Benefits

- Potential for decreased dysmenorrhea/improvement in symptoms of endometriosis
- Decreased menstrual blood loss for those with heavy periods
- Protection from endometrial cancer
- Decreased risk of pelvic inflammatory disease (from thickened cervical mucus)

Patient Selection

Good Candidates

- Motivated and adherent pill takers of all ages who are able to take the pill at the same time (±3 hours) every day.
- Patients with relative or absolute contraindications for estrogen-containing hormonal contraceptives such as increased risk for venous thromboembolic events.

- Patients with estrogen-related side effects, including nausea, breast tenderness, decreased libido, or headaches.
- Breast-feeding patients, as only small amount enters breast milk and POPs do not appear to affect a patient's milk supply.
- POPs have very few contraindications and can be used when appropriate after prior stroke (if not related to POP use), complicated valvular heart disease, viral hepatitis, migraine with aura, diabetes, hypertension, or older age with multiple risk factors for CVD or smoking.

Poor Candidates

- Patients who are unable to be adherent to the POP schedule
- Patients who cannot tolerate irregular bleeding or amenorrhea
- Patients with relative or absolute contraindications (see section "Contraindications to Use").

Available Options/Choosing the Best Option

Category Options

The synthetic progestins utilized in hormonal contraceptives including POPs are structurally related to testosterone. This includes the estranes (e.g., norethindrone) and gonanes (e.g., levonorgestrel and desogestrel). The majority of the POPs on the market contain norethindrone, and until 2019, this was the only POP available in the United States. All norethindrone POP packs contain 28 days of active pills with no hormone-free interval. In 2019, the FDA approved a drospirinone POP consisting of a pack of 24 active pills containing 4 mg drospirinone and 4 placebo pills. The company reports an improved bleeding profile and contraceptive efficacy for up to 24 hours in the event of a delayed or missed pill. Commercial launch is expected in 2019. This may be a good option for over-the-counter oral contraceptive pills in the future.

Contraindications to Use

There are few contraindications to POP use, and most patients are good candidates. With regard to thrombotic risk, it is important to distinguish those at higher risk of venous thrombosis from those at risk of arterial thrombosis. Progestins may cause a "male-type" cholesterol profile shift in users, leading to a drop in HDL and an increase in LDL. This, combined with an underlying high risk for arterial thrombosis, may mean that the risks of this method outweigh its benefits for certain patient groups, as described below.

Absolute Contraindications (Category 4 in the US Medical Eligibility Criteria [US MEC])

- Current breast cancer

Risks Generally Outweigh Benefits (Category 3 in the US MEC)

- Past history of breast cancer (no evidence of disease for 5 years)
- Since POPs are metabolized in the liver:
  - Liver disease with severe, decompensated cirrhosis
  - Liver tumors (hepatocellular adenoma or malignancy)
- If a patient develops:
  - Ischemic heart disease while on POPs
  - A cerebrovascular accident while on POPs
- Systemic lupus erythematosus and positive or unknown antiphospholipid antibodies, due to increased risk of venous and arterial thrombosis
- History of bariatric surgery with malabsorptive procedures, due to concern of decreased efficacy in case of malabsorption

Patient Educational Points

Counseling Tips

Instructions to Use

- POPs must be taken at the same time every day (±3 hours for norethindrone POPs).
- No pill break between pill packages (for norethindrone POPs).
- If a pill is taken more than 3 hours too late or missed, or in case of vomiting or diarrhea, patients should have a backup method available or abstain from sex for next 48 hours. Consider emergency contraception if unprotected sex within the past 3–5 days.
- For this reason, POP users should be educated about – and have access to – emergency contraception.
- Minor side effects, such as nausea or mood changes, may decrease after several cycles.
- Abnormal, unpredictable bleeding may be expected, but may improve over time.
- POPs offer no protection from STIs or HIV. Encourage condom use for patients at risk.

Patient Screening

A complete history should be obtained prior to initiation of contraception. A patient's preferences and previous experiences with birth control should always be taken into account prior to contraception initiation, as well as the patient's medical and gynecological comorbidities. Otherwise, there are no screening tests that are required prior to POP initiation. A pelvic exam or a Pap smear is *not* a prerequisite to prescribing hormonal contraception, including POPs.

Timing of Initiation

POPs may be started at any time if it is reasonably certain that a patient is not pregnant. Providers should recommend the use of a backup method (condoms or abstinence) for 2 days if the patient is at risk of ovulation. In case of switching from an IUD, ideally, providers should remove it within 5 days of the last normal period in order to minimize the risk of residual sperm from any recent unprotected intercourse leading to fertilization.

If there is uncertainty regarding a possible luteal phase pregnancy even though a pregnancy test is negative, the benefits of starting POPs still likely outweigh the risks. The POP can be started immediately with the recommendation to repeat a pregnancy test in 2–4 weeks.

No backup method is necessary if POPs are started during the following period:

- During the first 5 days of a normal menstrual cycle
- Less than 6 months postpartum if a patient is fully or nearly fully breast-feeding and amenorrheic
- Within the first 21 days postpartum if not a patient is not breast-feeding
- Immediately after an abortion
- The day after stopping another hormonal contraceptive method. If switching off COCs, skip placebo pills and start the POP the next day following the last COC pill
- On or before the date when the next depot medroxyprogesterone acetate injection would have been due
- When switching from an IUD within 5 days after a menstrual period

Dispensing the Method

Access to a greater number of pill packs at one time may improve adherence. Some family planning clinics, like the US-based Planned Parenthood Federation, provide patients with a year's supply at once. Although US-based insurance companies will honor a year's worth of refills, many patients have insurance plans that only allow

them to receive one pack of pills each month, and they must return monthly to the pharmacy to obtain their medication. However, these insurance plans may permit a 3-month supply through mail-order pharmacies.

Managing Problems

Disadvantages

In comparison to COCs, currently available POPs must be taken even more consistently at the same time each day in order to maximize effectiveness. There is no proven protection from sexually transmitted infections (STIs) and dual protection with condoms is recommended if needed.

Side Effects

- Menstrual disturbance in approximately 50% of cycles (short and irregular in 40%; amenorrhea in 10%).
- Breakthrough bleeding/spotting may account for 10–25% of POP users discontinuing use during the first year. POP users have a higher number of spotting/bleeding days than COC users.
- Functional ovarian cysts are more common in POP users compared with users of COCs.
- Possible androgenic side effects such as acne, oily skin, hair loss, or hirsutism.
- Infrequently: Nausea, decreased libido, breast tenderness.
- In case of a method failure/pregnancy, there may be an increased risk for an ectopic pregnancy.

The main side effect associated with POPs is a change in bleeding. Counseling patients prior to POP use regarding what to expect with regard to bleeding is critical. Bleeding patterns can vary from amenorrhea to regular monthly periods to irregular bleeding. All of these patterns can be normal. If bleeding patterns change and there is a concern for pregnancy, STI, or other gynecological abnormalities, then the appropriate workup should ensue.

Unfortunately, no evidence-based guidance exists regarding how to treat POP users with unacceptable bleeding patterns except for encouraging consistent use.

Warning Signs

Warning Signals

- Headache, chest pain, or neurologic changes can be warning signs of an arterial thromboembolic event.

Drug Interactions

Contraceptive effectiveness may be decreased by other medications that induce liver enzymes. These interactions *do not* diminish the effectiveness of the non-contraceptive drug. Key interactions include the following:

- Antiretroviral therapy: certain ritonavir-boosted protease inhibitors (US MEC Category 2 – benefits of the contraceptive method generally outweigh risks)
- Anticonvulsants: phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine (US MEC Category 3)
- Rifampicin or rifabutin (US MEC Category 3)

Further Reading

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Chapter 4
Transdermal Contraceptive Delivery Systems

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General Overview of Method

The transdermal contraceptive system (TDS or patch) is a highly effective, reversible method delivering either estrogen and progestin or progestin alone similar to oral contraceptives (OCs). The currently marketed TDS contains both ethinyl estradiol and norelgestromin (EE/NGM, Ortho Evra, Janssen Pharmaceuticals) and was approved by the US FDA in 2001. The EE/NGM delivers the hormones over a 1-week period of time and is indicated for the prevention of pregnancy. Besides having many of the same contraceptive and noncontraceptive benefits as combination oral contraceptives (COCs) containing both estrogen and progestogen, transdermal contraception has additional advantages such as lower peak serum concentrations after application, avoidance of first-pass hepatic metabolism, and a less frequent administration schedule resulting in increased compliance. The most common adverse events are application site reactions, breast discomfort, nausea, and headache. A new lower dose TDS (AG200-15: Twirla, Agile Therapeutics) under review at the FDA delivers 120 mcg levonorgestrel (LNG) and 30 mcg ethinyl.

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Current Option Ethinyl Estradiol/Norelgestromin Transdermal System (EE/NGM TDS, Ortho Evra)

The Ortho Evra patch is a thin, flexible, beige-colored, 20 cm^2 (1.75 $in.^2$), two-layered, matrix-type patch with a clear plastic backing that is removed before application (see Fig. 4.1).

The backing layer consists of an outer low-density pigmented polyester layer and an inner polyester layer. On the outside of the backing layer is a heat-stamped "ORTHO EVRA™ 150/20." This layer provides structural support and protects the inner layer from the environment. The inner layer contains the active medication and also a polyisobutylene and polybutene adhesive. There is a clear polyester film backing that protects the adhesive layer during storage and is removed just before placement.

The EE/NGM TDS contains 0.75 mg ethinyl estradiol (EE) and 6 mg norelgestromin (NGM) releasing 20 μg EE and 150 μg NGM. Norelgestromin which was previously known as 17-deacetylnorgestimate is the primary active metabolite of norgestimate. A plateau in serum levels of EE and NGM is reached at approximately 48–72 h after patch application. The serum concentration ranges from 23 to 138 pg/mL for EE and from 0.3 to 1.53 ng/mL for NGM, which is within the reference concentration ranges of 25–75 pg/mL and 0.6–1.2 ng/mL, respectively, for up to 10 days after application. Effective serum concentrations are achieved regardless of exposing the woman and application sites to heat, humidity, exercise, and cool water immersion. The half-life values of EE and NGM are 17 h and 28 h, respectively [1].

Overall exposure based on the area under the curve (AUC) concentration to EE and NGM with patch use was higher, but the maximal serum concentrations were lower compared to a COC. The AUC for EE in the TDS users was 60% higher compared to a 35 μg EE containing COC. These findings led to a concern about a

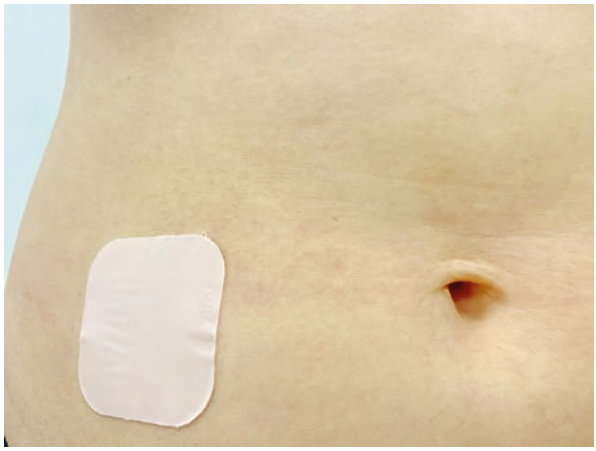

Fig. 4.1 A EE/NGM TDS on a model

possible higher risk for venous thromboembolism (VTE). The peak serum concentration of EE with the EE/NGM TDS was 35% lower, and the EE plasma concentrations were at a more constant level compared to a daily COC, the latter resulting in daily peak and trough levels of the hormones [2, 3].

The first-pass metabolism that occurs with COCs in the gastrointestinal tract and liver is avoided when EE and NGM are directly absorbed into the circulation by the transdermal application. Norelgestromin is metabolized to norgestrel and various hydroxylated and conjugated metabolites, while EE is metabolized to various hydroxylated products that are then conjugated with glucuronide and sulfate, and eliminated by renal and fecal pathways.

EE is extensively bound to serum albumin and when given orally induces an increase in the serum concentration of sex hormone-binding globulin (SHBG) that is not found with transdermal administration. Unlike its metabolite, norgestrel which is bound to SHBG, NGM is bound to albumin which results in 1.6-fold increased level of SHBG when taken orally. Endogenous androgens are bound to SHBG, leading to decreased circulating levels of free testosterone and dehydroepiandrosterone sulfate (DHEAS) [4].

New Option

A New Transdermal Contraceptive Delivery System: Levonorgestrel and Ethinyl Estradiol (Twirla, Agile Therapeutics)

This TDS contains EE and levonorgestrel (LNG) in an active matrix core of 15 cm^2 covered and surrounded by a perimeter adhesive system resulted in total area for the patch of 26 cm^2. The perimeter adhesive system, an overlay, is composed of an adhesive fabric, which was adhered to the back of the active portion of the patch to improve the adhesion characteristics. The adhesive mixture includes polyisobutylene, polybutene, polyvinylpyrrolidone, vinyl acetate, and heptane.

This system is called Twirla® or Agile Patch (AG) (Agile Therapeutics, Princeton, NJ, USA). It is also a once weekly application for 3 weeks followed by 1 week off. The Twirla patch [releasing 30 mcg EE and 120 mcg LNG] was approved by the FDA Feb 14, 2020 for women <30 kg/m^2. Previously, the only FDA-approved transdermal contraceptive patch containing EE and NGM was reported to have a higher area under the curve for EE than an OC containing 35 μg EE. This finding raised the concern of a possible increased risk of thrombotic and cardiovascular events. Because of this concern, a TDS containing a lower concentration of EE and levonorgestrel (LNG) was developed.

Three EE doses of the Agile Patch (AG200 LE: 15 μg EE/75 μg LNG; AG200-12.5: 20 μg EE/100 μg LNG; AG200-15: 25 μg EE/120 μg LNG) were compared to COCs containing 30 μg EE/150 μg LNG in phase 1 and phase 2 studies. All EE doses in the TDS demonstrated significantly lower maximum serum concentrations of EE while provided good cycle control with similar incidence of breakthrough bleeding or spotting to low-dose OC [5].

EE/LNG 25/120 μg was compared to a COC containing 35 μg EE and 250 μg NGM, which was also used as a comparator for the EE/NGM TDS. The EE/LNG TDS showed maximum concentrations of EE approximately 60% lower than the COC, resulting in a calculated EE daily dose equivalent to a COC with 30 μg EE [6].

There has been a concern related to contraceptive efficacy in women who weigh more than 90 kg (198 lb) [7]. A phase 2 study of the EE/LNG TDS focused on obesity and ovarian suppression using serum progesterone levels during the early and late phases of the TDS 21-day cycle during three treatment cycles. The EE/LNG TDS efficiently suppressed ovulation in both obese (body mass index [BMI] >30) and nonobese (BMI <30) women [8].

A further study of the pharmacokinetic profile of EE and LNG used three different application sites (lower abdomen, buttock, and upper torso) and found that the absorption of EE and LNG from all sites was therapeutically equivalent; however, application of the TDS to the lower abdomen had slightly lower serum levels compared to the other sites [9]. The EE/LNG TDS showed excellent adhesion during exposure to sauna, treadmill, whirlpool, or cool water emersion [10].

A contraceptive efficacy and safety study that compared the EE/LNG TDS to a 20 μg EE/100 μg LNG OC in 17- to 40-year-old women over 13 cycles reported a pearl index of 2.82 (0.98–4.67) among compliant (>80% use of the method) users. Reported side effects including nausea, vomiting, headache, increased weight, breast tenderness, acne, and dysmenorrhea as well as unscheduled bleeding and the severity of adverse events were not statistically significantly different between the TDS and COC [11]. The most common side effects which occur more than 10% for the EE/LNG TDS were headache, nausea, and application site reaction [6]. The phase 3 clinical studies for the EE/LNG TDS have been completed [12].

Other Combination TDS (Not Currently Available in the United States)

Gestodene and Ethinyl Estradiol Transdermal System (Bayer Healthcare)

A transdermal system containing a low-dose EE and gestodene (GSD) fabricated in five different layers within a polyisobutylene matrix for skin adherence is under clinical investigation. This TDS containing 0.9 mg EE/1.9 mg GSD in 10 cm^2 size TDS was studied during two menstrual cycles. Inhibit of ovulation was found in all subjects based on suppression of the luteinizing hormone mid-cycle surge, and after

cessation of treatment, ovulation returned in 85.7% of participants [13]. Another study compared EE/GSD patch with comparable doses to OC with 20 μg EE and 60 μg GSD. The patch is 11 cm^2 in size with 0.55 mg EE and 2.1 mg GSD per patch. A comparative study of the patch and low-dose OC showed well tolerability and comparable in hemostatic endpoint without significant hemostasis parameter changes during three cycles of study period. Side effects such as bleeding and spotting were reported by 6.7–30.8% of women using patch. However, contraceptive efficacy was not examined in this study [14]. A recent phase 3 multicenter study of this patch reported 0.81 adjusted pearl index and 98.8% probability of contraceptive protection after 364 treatment days with very high mean compliance of 97.9%. Incidence of intracyclic bleeding/spotting among users was 11.4% in cycle 1 and decreased to 6.8% in cycle 12. Common adverse events were headache and application site reaction reported as 9.5% and 8.5%, respectively [15].

Transdermal Progestin-Only Delivery Systems for Contraception

Three progestin-only transdermal contraceptive systems are under development. The advantage of these methods is the absence of estrogen in these products. Progestin-only oral contraceptive products do not increase the incidence of VTE [16]. A TDS containing norethindrone acetate only has progressed to an efficacy and safety trial.

Desogestrel Transdermal System

A study of desogestrel reported it to be significantly more permeable through the hairless rat skin than LNG in vitro. Physical characterization of the patch suggested that a uniform and reproducible patch used for 7 days could be developed [17].

AG1000-6.5: Levonorgestrel Transdermal System

A transdermal system containing LNG for a continuous 28-day regimen releasing either 75 or 40 μg of LNG daily [18] is under development.

Norethindrone Acetate Transdermal System

An open-label study of norethindrone acetate delivered via a transdermal contraceptive patch sponsored by Watson Pharmaceuticals studied its contraceptive efficacy, but no report is available (www.clinicaltrials.gov, NCT01140217).

Picking the Right Candidate for a Contraceptive Patch

Good Candidates

- Women who want a nonoral female-controlled reversible contraceptive method
- Women who have poor compliance with using a daily method
- Women with a condition that would derive a noncontraceptive benefit from using combined hormonal contraceptive such as androgen excess and dysmenorrhea

Poor Candidates

- Women with contraindications to use of estrogens and/or progestins
- Women with risk factors for thrombotic, cardiovascular and cerebrovascular disease such as age over 35 years with smoking and hypertension.
- Women on enzyme-inducing agents such as some types of anticonvulsant drugs since they could reduce contraceptive efficacy.
- Women with sensitive skin, dermatologic disorder, and skin allergy to patch adhesives.
- Obese women with weight equal to or more than 90 kg (198 lb) is controversial. Pooled data from three pivotal clinical studies suggested that the contraceptive efficacy of transdermal contraceptive patch (Ortho Evra) was less in women with a body weight of equal to or more than 90 kg (198 lb) since post hoc analysis indicated that 5 out of 15 pregnancies occurred in this subgroup, but body weight was not found to be related to contraceptive failure [7]. However, a Cochrane review concludes that the evidence is limited [19].

A recent report of the TDS EE 30 μg/LNG 120 μg (AG200–15) was shown to suppress ovulation in both obese and nonobese women with BMI >30 as obese [8].

Advantages

Contraceptive-Related Benefits for a Transdermal System

1. Convenience of use since it requires once a week dosing
   Incorrect use or dosing is a major cause of contraceptive failure. A patch offers significant greater perfect dosing than COCs (88.7% vs. 79.2%) and consistent compliance in all age groups (89.6–91.8%) [20]. Perfect use was consistent across all age groups for patch users, and significantly differed by age for COC users in the comparative study conducted in the United States [21]. Reported

compliance in COC users indicated that 39–65% missed at least one pill in 3-month period, and this incidence is highest in women aged 18–24 years old [22]. Accordingly, the transdermal contraceptive system is a good option for adolescents who have lower compliance rate with other methods. Comparing to COC, TDS users have better compliance with odds ratio (OR) of 2.05 (95% CI 1.83–2.29) and 2.76 (95% CI 2.35–3.24) [23]. Moreover, the contraceptive patch is reported to significantly reduce follicular size and ovulation comparing to COC even with dosing errors [24].

2. Other advantages

   Continuous and sustained release over a 1-week period of time

   – Avoids first-pass hepatic metabolism and enzymatic degradation by gastrointestinal tract
   – Rapidly reversible once patch removal
   – Verifiable, visible patch

Noncontraceptive-Linked Benefits

- Since patches have the same mechanism of action as COCs, they are expected to provide the same noncontraceptive benefits as follows.
- A therapeutic option for androgen excess
- Norelgestromin (NGM), a progestin component in transdermal contraceptive patch, is a derivative of norgestimate which contains minimal androgenicity [25]. Moreover, a study of transdermal contraceptive patch with EE/NGM showed association with decreased serum-free testosterone and DHEAS [4].
- Menstrual bleeding control
- Less cyclic mood changes, premenstrual syndrome
- Less dysmenorrhea
- Decreased risk of endometrial and ovarian cancer

Disadvantages of a Contraceptive Patch

- The patch is noticeable; privacy may be a concern.
- Skin irritation and hypersensitivity reactions can occur.
- Detachment of patch occurs 1–2% and requires replacement.
- Provides no protection against sexually transmitted disease (STD) and HIV.
- Replacement required weekly with a new patch.
- There are no generic equivalents and cost may be a concern.
- Room temperature storage is necessary.

Side Effects Associated with the Currently Available Transdermal Contraceptive Delivery Systems

The incidence of common side effects for a transdermal contraceptive patch was similar to that of OC from pooled comparative clinical study data. However, patch users have a higher incidence of application site reactions, breast symptoms, and dysmenorrhea [26]. The most common side effects leading to discontinuation were application site reactions (1.9%), nausea (1.8%), emotional lability (1.5%), headache (1.1%), and breast discomfort (1.0%) [27]. Patch users tend to discontinue its use because of side effects more than OC users [23].

- Breast symptoms 22% (breast discomfort, engorgement, and pain)
- Headache 21%
- Application site reaction 17.4%
- Nausea 26.8%
- Dysmenorrhea 10.1%
- Vaginal bleeding 6.4%
- Mood, affect, and anxiety disorder 6.3%

Serious Side Effects Related to a Transdermal Contraceptive Delivery System

- Thrombotic events

A large epidemiologic study of 297,262 women age 15–44 years old who started using the EE/NGM TDS or COC containing 35 μg EE and norgestimate reported the diagnosis of venous thrombosis or pulmonary embolism based on International classification of diseases (ICD) 9 records from the IMS/PharMetrics database, a US-based, ongoing longitudinal database from April 1, 2002, to October 31, 2007. The first study in 2006 reported venous thromboembolism (VTE) in contraceptive patch users with an odds ratio (OR) of 0.9 (95% CI 0.5–1.6) and the second study in 2007 reported an OR of 1.1 (95% CI 0.6–2.1) [28, 29]. A recent update of these studies identified 19 new cases of VTE among the contraceptive patch users and 30 μg EE/LNG COC users resulted in an OR of 2.41 (1.17–4.97). These data when combined with prior reports found an OR of 1.23 (0.86–1.77), leading to the study conclusion that transdermal contraceptive patch users have no increase VTE risk compared to COC [30, 31].

Another series of epidemiologic studies compared EE/NGM transdermal contraceptive users to COC users between April 1, 2002, and December 31, 2006, which reported more than twofold increase of VTE among patch users with incidence rate ratio of 2.2, 95% CI 1.3–3.8, or 40.8 cases per 100,000 woman-years. After excluding women with high-risk factors for VTE, the OR was still high at 2.4 (95% CI 1.1–5.5) [32]. An extended analysis of 598,431 women after exclusion of malignancy

(other than nonmelanoma skin cancer), coagulation defects, long-term anticoagulant use, history of VTE, chronic inflammatory disease, or chronic renal failure also reported a twofold higher risk of VTE among patch users (OR 2.0; 95% CI 1.2–3.3) compared to COC users [32, 33].

There are still conflicting data among studies whether the patch causes more risk of thrombotic event than COC. The concern about VTE led to a revision of product labeling [34]. However, all COCs increase the risk of thrombotic events; but VTE rates associated with pregnancy are even greater especially during postpartum period with absolute risk of 199.7 per 100,000 woman-years or relative risk of 4.29 (95% CI 3.49–5.22) [35].

- Serious cardiovascular events and stroke

  Cardiovascular events and stroke are rare among young women using hormonal contraceptives. An epidemiologic study comparing these events between the EE/NGM patch and 35 μg EE/norgestimate COC among 15- to 45-year-old users concluded that there was no increased risk of acute myocardial infarction or ischemic stroke among patch users, with an incidence rate ratio of 0.2 (95% CI 0.004–1.7) and 1.2 (95% CI 0.41–3.4), respectively [36]. Another study found no significant risk of stroke (OR 0.6; 95% CI 0.1–3.2) or acute myocardial infarction (OR 1.2; 95% CI 0.3–4.7) in EE/NGM patch users comparing with COC users [33].
- An increased risk of other conditions that have been associated with COC use can also be found in patch users such as liver disease (impaired liver function, hepatic adenoma, and liver tumors) and gall bladder disease (cholestasis).

Warning Signals Associated with Serious Adverse Events

- Thrombotic events: severe leg pain, sharp chest pain, shortness of breath, and coughing up blood
- Cardiovascular events: crushing chest pain and tightness in the chest
- Stroke: severe or increased frequency of headache, blurred vision, visual problem, speech problem, numbness, or weakness of arms or legs
- Liver and gall bladder disease: jaundice or yellowing of skin or eyeballs, dark-colored urine, and light-colored bowel movements

Reproductive Effects

- Fertility delay

As with COCs, there could be a few weeks of delay in return of ovulation in women discontinuing the use of the patch.

- Breakthrough bleeding

Most women started withdrawal bleeding on the fourth day of patch-free interval, and the median duration of bleeding was 5–6 days. Incidence of irregular bleeding among patch users is low and similar to COC users. One study showed significantly higher breakthrough bleeding and/or spotting in patch comparing to COC group in first two cycles but not significantly different in subsequent cycles [37]. In pooled data from comparative trials between patch and COC, the incidence of breakthrough bleeding in patch group was low and decreased overtime of use equivalent to COC group [7].

- Carcinoma of breast and cervix

Risks are assumed to be similar to those in COC users. The majority of studies showed small or no changes in relative risk of breast cancer with COC use. It appears that the dose or type of either steroid, as well as duration of COC use, is not related to breast cancer risk. Some studies suggested that COC use has been associated with increased risk of cervical cancer or cervical intraepithelial neoplasia. However, those findings may be due to different sexual behavior using COC instead of condoms to protect human papilloma (HPV) transmission, the main cause of cervical cancer.

Drug Interactions

A study on drug interaction between the EE/NGM contraceptive patch and 500 mg tetracycline orally every 6 h co-administered for a week showed no significant changes in EE or NGM serum concentration, thus concluding that tetracycline does not decrease patch efficacy [1].

Some drugs or herbal products are enzyme-inducing agents that could increase clearance of contraceptive steroids through interfering of liver enzyme pathway, for instance, cytochrome P450 and cytochrome P3A4. This group of drugs including barbiturates, sulfonamides, griseofulvin, phenylbutazone, phenytoin, carbamazepine, cyclophosphamide, rifampin, and St. John's wort should not be used with COCs or the transdermal contraceptive patch [38, 39]. In contrast, the use of contraceptive methods containing estrogen is classified as a category 3 for women on lamotrigine [Lamictal], as the estrogen increases the clearance rate of lamotrigine.

Contraindications [WHO/CDC Recommendations]

Absolute Contraindications

According to CDC recommendations US Medical Eligibility Criteria for Contraceptive Use, 2010 (US MEC), the transdermal contraceptive patch has the same contraindications to use as COCs [40, 41].

These contraindications are as follows:

- Hypersensitivity to any component of the product
- Undiagnosed genital bleeding
- Known or suspected pregnancy
- Postpartum less than 21 days
- Current breast cancer
- Acute or flare of viral hepatitis, severe cirrhosis, hepatocellular carcinoma, or malignant liver tumor
- A high risk of arterial or venous thrombotic diseases associated with the following conditions
  - Acute deep vein thrombosis (DVT) or pulmonary embolism (PE), history of DVT/PE with higher risk for recurrence, and major surgery with prolonged immobilization
  - Smoking equal to or more than 15 cigarettes a day in women over 35 years old
  - Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies
  - Thrombogenic mutations
  - Complicated solid-organ transplantation
  - Complicated valvular heart disease
  - Ischemic heart disease
  - Peripartum cardiomyopathy within 6 months or moderately or severely impaired cardiac function
  - Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension)
  - Diabetes mellitus with nephropathy, retinopathy, neuropathy, or other vascular disease of diabetes of more than 20-year duration
  - Hypertension with systolic blood pressure equal to or more than 160 mmHg or diastolic blood pressure equal to or more than 100 mmHg or with vascular disease
  - History of cerebrovascular accident
  - Headache with aura at any age

Relative Contraindications

Consider other methods in these conditions, since theoretical or proven risks usually outweigh the advantages.

- Past or no evidence of breast diseases for 5 years
- History of DVT/PE with lower risk for recurrence
- Cervical cancer or cervical intraepithelial neoplasia
- Symptomatic gallbladder disease
- Headache without aura and over 35 years old
- History of OC-related cholestasis
- Hyperlipidemia
- Adequately controlled hypertension and under 35 years old
- Inflammatory bowel disease
- Peripartum cardiomyopathy more than 6 months
- Postpartum between 21 and 42 days with other risk factors for DVT/PE
- Smoking less than 15 cigarettes a day and over 35 years old
- Some types of antiretroviral therapy (ritonavir-boosted protease inhibitors)
- Some types of anticonvulsant therapy (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine)
- Rifampicin or rifabutin therapy
- Weight more than 90 kg (198 lb) since efficacy may be a problem

Counseling Tips

Before initiation of a transdermal contraceptive patch, a complete history should be obtained to evaluate the potential patch user. Blood pressure should be measured to identify hypertension. In addition, baseline weight and body mass index (BMI) might be useful in monitoring and counseling since the efficacy might be decreased in women over 90 kg (198 lb). Clinical breast examination, bimanual pelvic examination, and cervical inspection are not necessary before initiation but recommended as usual annual screening. Other laboratory tests such as glucose, lipids, liver enzymes, hemoglobin, thrombogenic mutations, cervical cytology, and screening for STD or HIV could be done if indicated [40].

- The patch can be applied to one of the four areas of the body: the buttocks, abdomen, upper torso (front and back excluding the breasts), or upper outer arm. Every new patch is applied on the same day of the week, known as the patch change day.
- It is important that new patches are placed in a new location each time.
- The patch change day can be identified on the dial in the storage case.
- No creams, lotions, powders, makeup, or other products should be applied to the skin where the patch will be placed.

- Patch offers no protection from STDs (no protection from lower tract transmission and infection).
- Minor side effects, such as breakthrough spotting or bleeding, breast tenderness, nausea, and mild headache, may decrease after several cycles.
- If a user misses the timely placement of the patch at the start of a patch cycle, apply the first patch of new cycle. This is now the new patch change day. Backup contraception should be used for 1 week.
- If a user misses new patch placement in the middle of the patch cycle, for up to 48 h late, apply the new patch immediately. The next patch should be applied as usual. No backup protection needed. (Patch has 2-day grace period in steroid release.)
- If a user is more than 48 h late to place new patch, start a new cycle; this is now the new patch change day; backup contraception is needed for 1 week.
- If a user forgets to remove a patch at the end of a patch cycle, user should remove the patch and start the next cycle on the usual patch change day.
- There should never be more than 7 patch-free days. If there have been more than 7 patch-free days, backup contraception is needed for 7 days.
- If the user wishes to change the patch change day, she should complete her current cycle and remove the third patch on the correct day. During the patch-free week, she should apply the new patch on the "selected" day, before the normal date, and this becomes the new patch change day. In no case should there be more than 7 consecutive patch-free days.
- Lack of withdrawal bleeding for one cycle: user may continue using patch if she has adhered to the prescribed schedule.
- If user has missed two consecutive periods (no bleeding or spotting), pregnancy should be ruled out.

Instructions to Use

- Apply a patch to clean, dry, and nonirritated skin on the upper outer arm, abdomen, buttock, or back. Do not apply a patch on the breasts [42].
- A new patch is replaced on the same day weekly for 3 weeks followed by 1 week off. Withdrawal bleeding should occur during the patch-free fourth week.
- Half the protective liner is peeled away and the sticky surface is applied to the skin. The other half of the liner is removed and the patch is pressed firmly with the palm of the hand for 10 s.
- Make sure that the patch is firmly placed making sure that all the edges are sticking and that the patch remains smooth after application.
- Check the patch every day to make sure it is in place and does not appear to be detached. In pooled data from clinical studies, 1.8% of patch fell off and 2.9% partially detached and 4.7% were replaced with a new patch. Various activities such as heat, humidity, and exercise do not affect patch adhesion [43].

If a patch is partially or completely detached, do not use supplemental adhesives or wraps to hold the patch in place.

If patch detachment occurs less than 24 h, reapply the same patch or replacement patch immediately, no backup contraception necessary.

If patch detachment occurs more than 24 h or unsure duration, start a new cycle immediately by applying a new patch and establishing a new patch change day. Backup contraceptive method must be used for 1 week of the new cycle.

- Extended use for transdermal contraceptive patch is an off-label use due to concern about an increase in thrombosis risk. A clinical trial that evaluated bleeding pattern in women with weekly patch application up to 12 weeks compared to cyclic use showed significant fewer median bleeding days, bleeding episodes, and bleeding or spotting episode in extended use regimen. Median time to first bleeding for extended use was 54 days comparing to 25 days with cyclic use. Women with extended use reported more side effects leading to 10% discontinuation. However, the women were satisfied with both regimens [44].

Timing of Initiation

- There are three options to start using a transdermal contraceptive patch, first day start, Sunday start, and quick start. With first day start, when user applies the first patch within the first 24 h of onset of menstrual period, there is no need for backup contraceptive. User can also choose Sunday start which is applying the first patch on the first Sunday after onset of menstrual period or quick start to initiate patch use anytime as long as pregnancy is excluded. With Sunday start and quick start, nonhormonal backup contraceptive method such as a condom, spermicide, or diaphragm is required during the first week of TDS use in the first cycle. Otherwise, a new user could choose to be abstinent during the first week [42].
- Adolescents: Initiate after three regular menstrual cycles.
- Post first-trimester abortion or miscarriage: Start immediately; if not started within 5 days, user should follow the instructions for a women starting for the first time and use backup contraceptive method during the first week since ovulation may occur within 10 days of an abortion or miscarriage.
- Post second-trimester abortion or miscarriage: Start after 4 weeks.
- Postpartum nonbreastfeeding: Initiate after 3 weeks postpartum.

The use of combined hormonal contraceptive before 3 weeks postpartum is contraindicated due to an increased risk of venous thromboembolism [45].

- Breastfeeding: Initiate after 4 weeks postpartum.

If menstrual cycle has not returned in 21 days postpartum, a user should use backup contraceptive method during the first week.

According to CDC recommendations; the US Medical Eligibility Criteria (US MEC) for contraceptive use in 2010, the transdermal contraceptive patch has the

same contraindications as COCs [40, 41]. However, a double-blind randomized controlled study comparing progestin only and COCs started at 2–8 weeks postpartum showed no difference in breast feeding continuation [46].

- Switching from COCs or a vaginal contraceptive ring: Start patch on the day user would normally start the next pill or insert the next ring or start on the first day of withdrawal bleeding but no later than 5 days after last active pill; otherwise, backup contraceptive method is used during the first week.
- Switching from progestin-only pill: Start on any day after stopping progestin-only pill, and use backup contraceptive method if it has been more than 5 days since first day of menstrual bleeding.
- Switching from depot-medroxyprogesterone acetate (DMPA). Start patch on any day before the next injection schedule or first Sunday before the next injection schedule.
- Switching from implant: Start immediately on the day of implant removal.
- Switching from intrauterine device: Start immediately on the day of intrauterine device removal, and backup contraceptive method is required to use during the first week, unless device removal is on the first day of menstrual period.

Managing Side Effects

- Application site reaction

If there is skin irritation, the patch may be removed and a new patch may be applied to a different location until the next schedule change day. Any residual adhesive can be removed with baby oil. Reconfirm that the patch is always placed on clean dry skin and at least 1–2 h after a shower or bath.

- Menstrual irregularity

Breakthrough bleeding and or spotting is common during first 1–3 months after initiating a contraceptive patch but will improve overtime [7]. If bleeding or spotting persists longer than a few cycles, the consumer and practitioner should consider other possible causes. If there is no withdrawal bleeding for two consecutive cycles, pregnancy should be ruled out.

Clinical Effectiveness

Contraceptive efficacy of transdermal contraceptive patch is reported to be high comparable to that of COCs based on three clinical studies [27, 37, 47]. The occurrence of unintended pregnancy during the first year of perfect use and typical use of the patch is 0.3% and 8% and equivalent to COCs. Pearl indices were 0.88 for perfect use and 0.7 for typical use. Overall and method failure rates during 13 cycles were 0.8% and 0.6%, respectively [7].

Contraceptive efficacy was significantly higher in cycles with perfect dosing (pearl index 0.83) than in those with imperfect dosing (pearl index 6.32), and the percentage of cycles with perfect dosing was higher in patch users than in COC users: 88.7% and 79.2%, respectively [20].

However, the efficacy of the contraceptive patch (Ortho Evra) was less in women with a body weight of equal to or more than 90 kg (198 lb) [7].

Mechanism of Action

- The contraceptive patch has the same mechanism of action as COCs which decreases gonadotropin release, thus inhibiting the mid-cycle luteinizing hormone surge and preventing ovulation [48].
- Prevention of follicular development due to FSH suppression during the follicular phase.
- Changes in cervical mucus resulting in viscid, thick, and scanty mucus, which prevents sperm penetration and inhibits sperm capacitation.
- Decrease in tubal motility, which increases or delays ova and sperm transportation.

Tips on Cost and Insurance Issues

The contraceptive patch is covered by most major managed care formularies. Basic information about prescription drug coverage can be checked at www.fingertipformulary.com. However, there are assistant programs providing discounted or free prescriptions for women without prescription drug coverage at www.access2wellness.com.

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Chapter 5
The Contraceptive Vaginal Ring

Rachel S. Mandelbaum and Donna Shoupe

Introduction

Nearly 1 million women in the United States use the contraceptive vaginal ring (CVR) [1]. CVRs provide highly effective and easily reversible contraception, with similar efficacy to other combined hormonal contraceptives (CHCs) and also several unique advantages. The CVR does not require daily patient adherence and is both discrete and user-controlled, allowing a woman to self-initiate or discontinue at any time without dependence on a health-care provider. After reaching steady state, circulating serum hormone levels are lower than those with combined oral contraceptives (COCs) and do not have daily fluctuations. This is due to constant rapid absorption via the vaginal epithelium and improved bioavailability with avoidance of the first-pass effect of liver metabolism. Cycle control with the ENG/EE CVR is excellent; the bleeding pattern is highly predictable with low rates of breakthrough bleeding and spotting.

There are currently three CVRs worldwide. Most widely used is the ENG/EE ring (NuvaRing), which was approved by the United States Food and Drug Administration (FDA) in 2001 after almost 20 years of development. The ENG/EE ring, which releases 120 mcg of ENG and 5 mcg of EE daily, is designed for use in a 28-day cycle including a 7-day hormone-free interval. Extended regimens may

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also be used and have been studied extensively. A second combined CVR, the SA/EE ring (Annovera), was just recently approved in August 2018 after nearly a decade of clinical trials funded by the Population Council and National Institute of Child Health and Human Development (NICHD). The SA/EE ring is used in a similar fashion as the ENG/EE ring, but it can be reused for a total of 13 cycles. It is not yet commercially available for use but is expected to be available in the contraceptive market within the next year. A progesterone-only vaginal ring, the Progering, is also available in several countries in South America for use in postpartum lactating women. This chapter focuses primarily on the ENG/EE ring, the only commercially available CVR in the United States, and also covers the SA/EE ring, given its recent FDA approval.

History of CVRs

One of the earliest descriptions of vaginal administration of substances for medicinal or contraceptive purposes dates back to the Kahun Gynecological Papyrus from ancient Egypt around 1825 BC, which details vaginal use of honey, carbonate salts, and crocodile dung for various ailments and/or contraception [2]. In modern times, David I. Macht was the first to formally publish on vaginal absorption of a variety of compounds, including alkaloids, esters, and antiseptics in 1918 [3]. Nearly half a century later, in 1964, Folkman and Long established the concept of controlled drug release from silicon polymers when they demonstrated that anesthetics encased in silicon rubber functioned to induce anesthesia in rabbits [4]. The use of silicon systems for prolonged drug administration was then applied to steroid hormones shortly thereafter by Dziuk and Cook, who suppressed the menstrual cycles of ewes with progestin-containing subcutaneous silicon implants [5].

In 1970, Dr. Daniel Mishell published a landmark proof-of-concept study of the first hormonal CVR; he used a ring containing medroxyprogesterone acetate to successfully suppress ovulation in three women over 28 days of use [6]. Employing this new strategy for contraception, the World Health Organization (WHO) developed a levonorgestrel (LNG)-releasing CVR in the mid-1970s. In subsequent multicenter clinical trials of this LNG ring, high discontinuation rates were observed due to menstrual disturbances, vaginal symptoms, and repeated expulsion of the ring [7]. Mishell then developed the first combined ring containing both estradiol and norgestrel in 1978; the new combined ring with the addition of an estrogen component had improved menstrual bleeding patterns, impressive efficacy in suppressing ovulation, and good clinical acceptance [8].

Over the subsequent two decades, a multitude of combined CVRs were under investigation containing several formulations and dosages of estrogen and progestins as well as different ring dimensions [9–11]. In the late 1970s, the Population Council, an international nonprofit nongovernmental organization dedicated to innovations in family planning, developed a CVR containing both LNG and estradiol. Although highly effective, further studies reported that it had negative effects

on lipid levels, including reductions in high-density lipoproteins and an increased risk of atherosclerosis in animal studies [12–14]. Study of another CVR containing norethindrone acetate and ethinyl acetate was abandoned due to high incidence of nausea and vomiting in the first cycle [15].

Finally, in the early 1990s, a ring containing etonogestrel (ENG) was developed by NV Organon in the Netherlands. ENG did not have the atherogenic or thrombotic properties of prior progestins studied in vaginal rings and had lower androgenicity, making it an excellent candidate for use in a CVR. The ENG/EE ring, branded the NuvaRing, was first approved in the Netherlands in February 2001, followed by other countries in the European Union in June 2001 and the U.S. FDA in October 2001. The ENG/EE ring (Nuvaring) was first marketed in the United States a year later in 2002. Two initial large, open-label, noncomparative studies conducted in the United States, Europe, and Canada by Roumen et al. and Dieben et al. in 2001 and 2002, respectively, yielded excellent contraceptive efficacy [16, 17]. These findings were confirmed in phase III studies when the ENG/EE ring was compared to standard COCs with several advantages, leading to the widespread use of the ENG/EE ring in the years to follow [18–20].

Segesterone acetate (also called nestorone, NES) was evaluated for use in a combined CVR in clinical trials even prior to the 1970s given its favorable metabolic profile, excellent suppression of ovulation, and low androgenic or estrogenic activity [11, 21–23]. A decade after initial studies on a nestorone combined CVR, the Population Council sponsored a 1-year dose-finding multicenter trial in 2005, and a ring containing NES 150 mcg/day and EE 15 mcg/day was then selected for phase III trials beginning in 2006 [22]. Two phase III trials enrolled a total of 2,308 women across 27 study sites in the United States, South America, Europe, and Australia [24–27]. These results were the basis for FDA approval of the SA/EE ring in August 2018 [25].

Specifications and Pharmacokinetics

The ENG/EE ring (NuvaRing) is a flexible, soft, and transparent vaginal ring made of ethinyl vinyl acetate. It has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm (Fig. 5.1a). The ENG/EE ring contains 11.7 mg ENG and 2.7 mg EE, and it releases 120 mcg/day of ENG and 15 mcg/day of EE over a 21-day period [18]. ENG, also called 3-keto-desogestrel, is a third-generation progestin that is the biologically active metabolite of desogestrel, a progestin found in several oral contraceptive pills. Etonogestrel is also the same progestin used in the available subdermal implant Nexplanon. It has a much lower androgenicity profile than LNG, a second-generation progestin.

Vaginal administration of ENG and EE allows for continuous dosing and results in low stable serum hormone concentrations. After initial insertion of the ENG/EE ring, absorption of ENG and EE through the vaginal mucosa is rapid; therapeutic levels are reached in the first day of use. Maximum serum concentration of ENG is

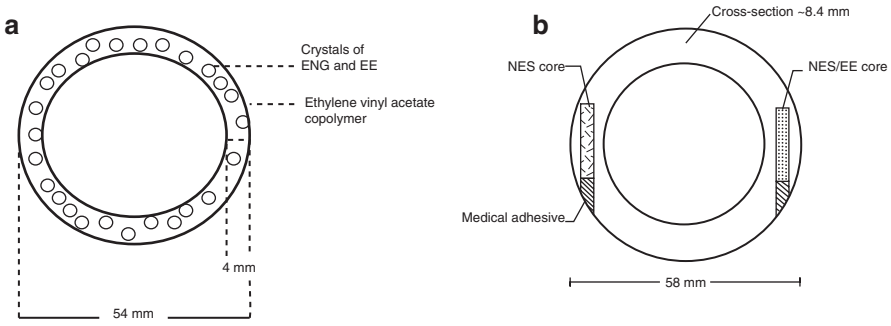

Fig. 5.1 Schematic of the ENG/EE (**a**) and the SA/EE (**b**) CVRs. (Adapted with permission from Kerns et al. [28])

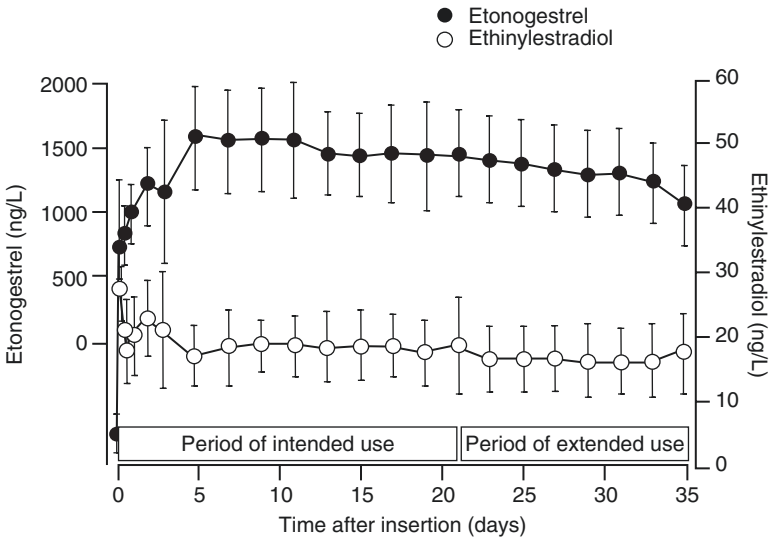

Fig. 5.2 Serum hormone levels are steady and remain therapeutic for at least 35 days. (Adapted with permission from Timmer et al. [29])

1,716 ng/L, which is reached within 7 days following placement [29]. Maximum serum concentration of EE is 34.7 ng/L, which is reached within 2–3 days following placement [29]. ENG and EE levels decline gradually thereafter but remain therapeutic at levels sufficient to inhibit ovulation for up to 35 days and potentially as long as 42 days during extended use regimens (Fig. 5.2) [29, 30]. Compared to desogestrel/EE COCs, bioavailability of ENG and EE with the CVR is 100% and 56%, respectively, compared to 80% and 54% with oral administration [29]. Maximum ENG and EE concentrations with the CVR were 40% and 30% of those seen with oral administration, respectively, and only occurred once per month compared to daily with COCs (Fig. 5.3) [29]. When comparing EE concentrations

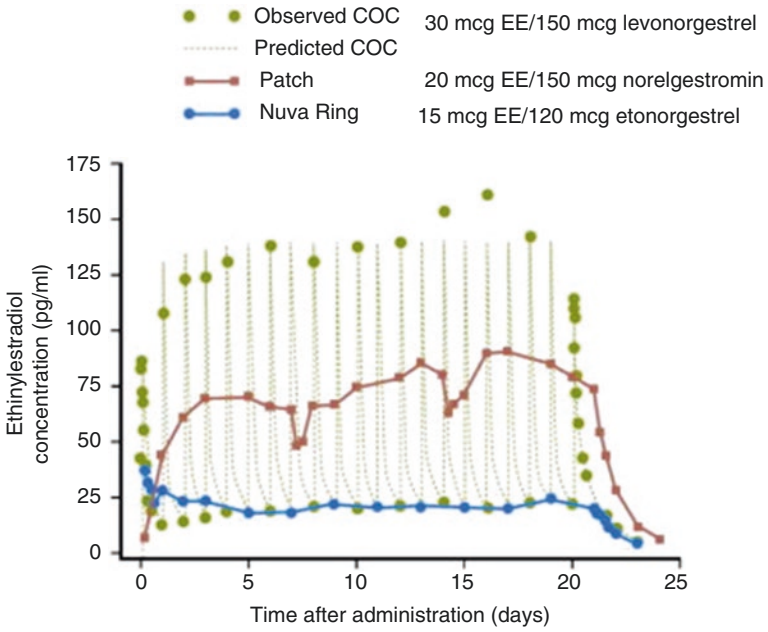

Fig. 5.3 Comparison of EE pharmacokinetics between COCs, the patch, and the NuvaRing. (Adapted with permission from Kerns et al. [28, 31])

between COCs, the patch, and the ENG/EE ring, exposure to EE with the ENG/EE ring was 3.4 times lower than with the patch and twice as low as with COCs (Fig. 5.3) [31]. Local concentrations of ENG and EE in the endometrium are also lower in CVR users when compared to COC users [32].

The half-life of ENG and EE is 19.3 and 44.7 hours, respectively [33]. Both ENG and EE are metabolized by the liver cytochrome p450 (CYP) isoenzyme 3A4 by hydroxylation and conjugation to sulfate or glucuronide groups. Hydroxylated ethinyl estradiol metabolites have weak estrogenic activity, whereas the biological activity of etonogestrel metabolites is unknown. Both are excreted primarily via the kidneys but also in the feces.

The SA/EE ring is a flexible, opaque white ring made of silicone elastomers that releases 150 mcg/day of SA and 13 mcg/day of EE (Fig. 5.1b) [22, 34]. It is designed to release hormones for a total of 273 days, equivalent to 13 cycles of 21-day intervals of wear followed by a 7-day hormone-free period during which the ring is removed [22]. The ring is 56 mm in overall diameter and 8.4 mm in cross-sectional diameter. There are two 3 × 27 mm channels that contain hormone-releasing cores, one releasing SA alone and the other releasing both SA and EE [22]. Each ring contains 103 mg of SA distributed throughout both cores and 17.4 mg of EE in only one core [34].

Maximum serum concentrations of SA and EE are 1,147 pg/mL and 129 pg/mL, respectively, which occur during cycle 1 and then gradually decline to

concentrations of 294 pg/mL and 39 pg/mL, respectively, by cycle 13. Time to maximum concentration is about 2 hours after placement. SA, similar to ENG, is metabolized by CYP3A4 to inactive metabolites, with a half-life of 4.5 hours [34].

Clinical Use

Insertion

The ring can be compressed into a more linear shape for manual placement or placed with an applicator. Placement can be performed in any position comfortable for the woman. Vaginal orientation is nonspecific as long as the ring maintains direct contact with the vaginal epithelium.

Initiation

If a woman is reasonably certain that she is not pregnant, the ENG/EE ring can be inserted by the patient into the vagina at any time in the menstrual cycle [33]. Even in cases in which the provider is uncertain whether the patient is pregnant or not, the benefits generally exceed any risk. A follow-up pregnancy test in this situation is recommended in 2–4 weeks. Below are instructions regarding initiation of the CVR [33, 34]:

Women not switching from another method:

- Initiation of the ENG/EE ring is recommended on the first day of menstrual bleeding; if inserted after, a backup contraceptive method is recommended for 7 days.

Women who switch to the CVR from other methods:

- From COCs: Women can discontinue pills at any time during the cycle and insert the ring immediately to begin a 21-day cycle. If more than 7 days elapses between discontinuation of hormonally active pills and starting the CVR, a backup method should be used for 7 days.
- From depo-medroxyprogesterone acetate: Women can start the ring on any day up until the date on which the next injection is due; if started after this date, a backup method should be used for 7 days.
- From hormonal or nonhormonal IUD: The CVR should be placed on the day of removal and a backup method used for 7 days.
- From implant: The CVR should be placed on the day of removal and a backup method used for 7 days.

After a miscarriage or abortion:

- The CVR can be initiated immediately.
- If delayed by more than 5 days, a backup method is recommended for 7 days.

Postpartum women:

- Due to the risk of venous thromboembolism (VTE) following pregnancy, it is recommended to delay initiation of combined hormonal contraceptives (CHCs).
- Women *without* risk factors for VTE (mentioned below) can consider initiation of the CVR at 21 days postpartum if not breastfeeding and at 30 days postpartum if breastfeeding, although it may suppress lactation.
- Women *with* risk factors for VTE (cesarean delivery, age ≥35, prior VTE or thrombophilia, immobility, preeclampsia, postpartum hemorrhage at delivery or recent transfusion, peripartum cardiomyopathy, body mass index [BMI] ≥30, tobacco use) should wait until 42 days to initiate the CVR.

Removal

The CVR is left in place continuously for 21 days and then removed for a 7-day hormone-free interval [28, 33]. During the 21 days in which the ring is in place, it may be removed for up to 3 hours at a time; if removed for more than 3 hours, a backup method of contraception is required for 7 days. After 21 days, the ENG/EE ring package insert recommends removal of the CVR for a withdrawal bleed. Withdrawal bleeding is expected 2–3 days following removal and may continue beyond the 7-day hormone-free period. A new ring should be inserted 7 days following removal. A backup contraceptive method is recommended for any hormone-free interval greater than 7 days [33].

Women desiring amenorrhea or suppression of menstrual-related conditions (endometriosis, menstrual migraine, and premenstrual mood changes) can be advised to follow continuous dosing with use of a single ring for 28 days following by immediate replacement with a new ring each month.

Removal is accomplished either by hooking a finger around the ring or grasping it between two fingers and pulling gently. It can be rinsed with cool to lukewarm water, however, hot water should be avoided.

SA/EE Ring

The use of the SA/EE ring is identical to that of the ENG/EE ring with the exception that it can be reused for up to 13 cycles without need for replacement [34]. After the 21-day cycle, the SA/EE ring should be removed and stored in a clean and dry place

until replacement 7 days later. The package insert recommends a backup method of contraception be used for 7 days if the SA/EE ring is removed for more than 2 consecutive hours compared to 3 hours for the ENG/EE ring.

Mechanism of Action

The primary mechanism of action of the CVR is inhibition of ovulation by suppression of gonadotropins. As with other CHCs, estrogen and progestins synergistically act at the level of the hypothalamus via negative feedback mechanisms to decrease pulsatile secretion of gonadotropin-releasing hormone (GnRH), thereby decreasing secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [35]. Without stimulation from FSH, follicle development is suppressed, and estradiol levels do not increase in the manner necessary to cause an LH surge. In the absence of the LH surge, ovulation does not occur. Estrogen also acts to stabilize the endometrium for the added benefit of cycle regulation and minimizing breakthrough bleeding. Progestins thicken cervical mucus, alter tubal peristalsis, and reduce endometrial receptivity due to reduced glycogen production and decreased gland proliferation.

Timmer and Mulders examined the effect of the ENG/EE ring on follicular development using vaginal ultrasound and laboratory serum concentrations of FSH, LH, estradiol, and progesterone. Complete inhibition of ovulation was observed with recommended use (3-week cycle) and maintained for an additional 2 weeks when use was extended to 5 weeks (Fig. 5.2) [29, 36].

The CVR is not approved for emergency contraception and does not afford protection against sexually transmitted infections.

Clinical Efficacy

Studies have consistently reported high contraceptive efficacy with CVRs, comparable to that of COCs and the patch but less than that of long-acting reversible contraceptive (LARC) methods due to the fact that it is user-dependent. One-year pregnancy rates for all CHCs are reported to be 8–9% with typical use and 0.3% with perfect use [1].

The Pearl Index, defined as the number of contraceptive failures per 100 women-years of exposure, for the ENG/EE ring has ranged from 0.25 to 1.23 over nearly two decades of study and was 2.98 for the SA/EE ring in a recent multicenter phase III trial [26, 27, 37]. In the initial phase III studies of the ENG/EE ring including over 2,000 women, the Pearl Index ranged from 0.77 (95% CI 0.37–1.40) to 0.96 (95% CI 0.20–2.82) with perfect use and from 1.18 (95% CI 0.73–1.80) to 1.23 (95% CI 0.40–2.86) with typical use [17, 20]. Similarly, in the recently released phase III trial of the SA/EE ring, the Pearl Index with perfect use was 2.10 (95% CI

1.37–3.06) when women did not remove the ring for periods >2 hours during the 21-day cycle compared to 5.89 (95% CI 3.46–9.27) when women reported instances of ring removal for >2 hours during the 21-day cycle [27]. The Pearl Index also varied by age; it was highest among women aged 18–19 years (8.15, 95% CI 3.50–15.8) and lowest among women >35 years of age (0.99, 95% CI 0.06–4.34).

Nearly half of women in the United States who have an unintended pregnancy are improperly using a form of contraception in the month of conception, highlighting that adherence is crucial to contraceptive efficacy. In the studies referenced above, the majority of pregnancies with the ENG/EE ring or SA/EE ring occurred in women who did not adhere to the recommended regimen [38]. Adherence to CVR recommended regimens for both the ENG/EE and SA/EE rings is estimated to be 80–90%; women report delays in ring replacement after temporary removal, forgetting to remove the ring after 21 days leading to ring use beyond 3 weeks, as well as forgetting to replace a new ring after the 7-day hormone-free interval [19, 27, 39].

While most method failures occur in women using the CVR incorrectly, in a study examining the effectiveness of the ENG/EE ring when use deviated from the prescribed regimen of 21-day use with a 7-day hormone-free interval, the ENG/EE ring still maintained impressive effectiveness. Delayed placement of the ENG/EE ring up to 10 days after the last menstrual period did not interfere with ovulation inhibition in contrast to delays in resuming COCs [40]. When examining variation in the timing of placement during the follicular phase, the maturation of follicles up to 13 mm in size was halted without progression to ovulation [40]. Placement for only 3 days was sufficient to suppress the hypothalamic–pituitary axis to inhibit ovulation in a similar manner to when it was used for the recommended 3 weeks [40]. Resumption of ovulation after the ENG/EE ring was removed was found to take a median of 19 days, which was similar whether the ring was used for 3 days or 3 weeks [40].

Factors Affecting Clinical Efficacy

In light of the obesity epidemic, knowledge regarding the efficacy of the CVR in obese women is of utmost importance but remains limited. Drug metabolism may differ in obese individuals compared to those of normal weight, potentially causing alterations in contraceptive efficacy. Ambiguity regarding contraceptive efficacy in obese women also exists due to the fact that contraceptive development studies have historically excluded obese women. In a study examining the pharmacokinetics of the ENG/EE ring in obese women compared to women of normal weight, EE levels were lower among obese women but had a similar rate of decline while ENG levels were not significantly different between the two groups (Fig. 5.4) [41]. Ovulation was completely suppressed in both obese women and women of normal weight as evidenced by follicular development and progesterone levels [30, 41]. In a recent phase III study of the SA/EE ring, the Pearl Index was 2.85 (95% CI 2.05–3.85) in women with a BMI ≤29 compared to 2.65 (95% CI 0.44–8.18) in those with a BMI

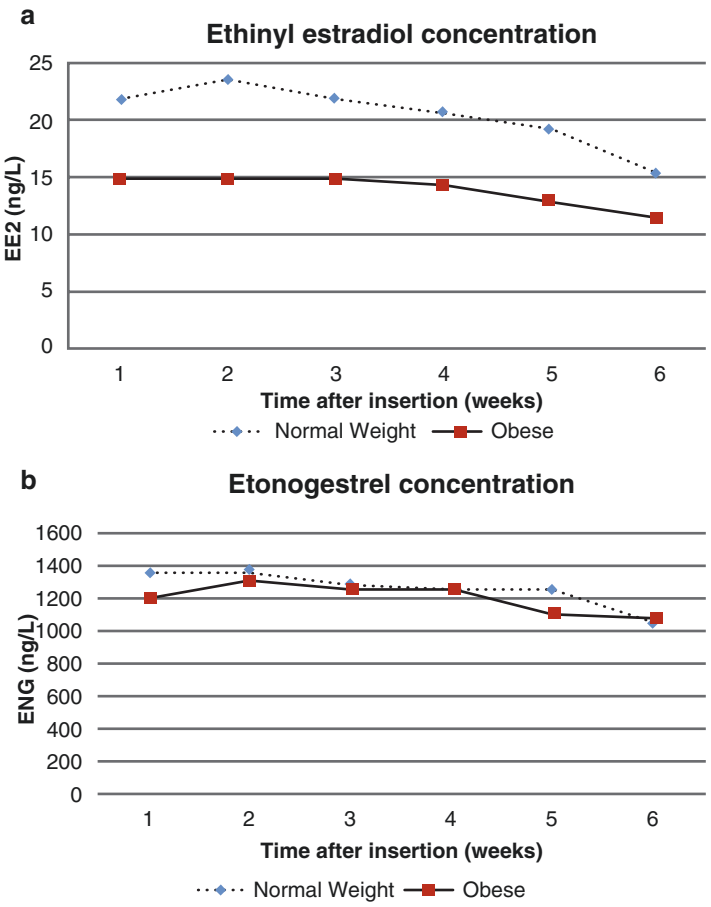

Fig. 5.4 EE and ENG levels in obese women and women of normal weight after ENG/EE ring insertion. (**a**) Mean ethinyl estradiol concentration. (**b**) Mean etonogestrel concentration. (Adapted from Dragoman et al. [30])

>29. These results are encouraging to support CVR use in obese women, although the use has not yet been studied in morbidly obese women with BMI >40. Further studies are warranted to determine the effect of BMI on CVR efficacy, particularly in those who are morbidly obese.

Multiple other factors that were initially of concern with CVR use have been reported to have minimal impact on contraceptive efficacy. Tampon use while the CVR is in place does not result in any changes in serum ENG or EE concentrations [42]. Nonoxynyol-9 in spermicides also does not affect EE or ENG release, absorption, or serum levels [43]. Oral ampicillin and doxycycline do not compromise efficacy of the CVR [44]. Finally, in studies of the ENG/EE ring and SA/EE ring, antimycotic medications, specifically miconazole nitrate, were reported to increase systemic hormone levels of EE, SA, and ENG [45, 46]. This effect was more

pronounced with the use of vaginal suppositories compared to a cream. While women with candidiasis using CVRs can be advised to use oral formulations of these medications, these changes are not expected to influence efficacy or tolerability.

Patient Satisfaction

Overall, the majority of women are satisfied with the CVR as a contraceptive method [19, 26, 47]. In the initial open-label noncomparative studies of the CVR in Europe and North America, satisfaction rates were very high. Of all participating women, 85% were satisfied or very satisfied with the ring, and 90% (97% in women who completed the study and 75% in women who prematurely discontinued the study) indicated that they would recommend the ring to others [16, 17]. In a subsequent study in the Netherlands, the most frequently reported reasons for high patient satisfaction were once-a-month administration, low hormonal dose, and ease of use. The most frequently reported reasons for dissatisfaction were general adverse events (16%), local adverse events like expulsion (8%), and/or inconvenience during intercourse (7%) [39].

Studies evaluating patient satisfaction with the CVR report similar or better results when compared to COCs or the patch. A large international study that included 1,950 women from the United States, Canada, Germany, Austria, Norway, Sweden, Denmark, Finland, France, the Netherlands, Belgium, Spain, the United Kingdom, and Israel was performed to determine acceptability and satisfaction with the CVR. At study intake, 66% of participants preferred COCs, but after three cycles of ring use, 81% preferred the ring [48]. Another study in women with a history of COC use who desired to switch to a nondaily contraceptive method also reported improved satisfaction rates with the CVR compared to the patch (71% vs. 27%, respectively) [47]. Women in this study had higher satisfaction with current ring use when compared to their prior COC use, while women were less satisfied with current patch compared to prior COC use. In another study that randomized women to 13 cycles of the ENG/EE ring or a COC containing EE and drospirenone, patient satisfaction was very high and comparable in both groups (84% vs. 87%) [19].

Continuation

Discontinuation of hormonal contraceptives is common due to a variety of reasons, which may or may not be related to patient satisfaction. Usually, over 30% of women can be expected to discontinue a hormonal contraceptive within the first year. Discontinuation rates overall for the CVR appear to be similar to or lower than rates of other CHCs in most studies.

In the two large, initial, noncomparative studies on the ENG/EE ring from Europe and North America, one-year discontinuation rates were reported to be

28–35% [16, 17, 19, 20]. About half of those who discontinued the ENG/EE ring (10–15% of all users) cited adverse effects, either device-related or systemic, as the reason for discontinuation. Less than 1% discontinued for bleeding irregularities. Most women who discontinued the CVR did so within the first three to four cycles of use [16, 17].

In the Contraceptive CHOICE project, a prospective cohort study of 10,000 women desiring contraception for at least 1 year, continuation rates of non-long-acting reversible contraceptives (non-LARCs) were lower than those for LARCs in women of all ages. For the CVR, 12-month and 24-month continuation rates were 56% and 41%, respectively, which were similar to those observed for the patch and COCs [49]. In the APPROACH study, a Spanish prospective multicenter study of 3,443 women, the 12-month continuation rates were similar for the CVR (42%) and COCs (46%), both of which were higher than the patch (26%) [50]. A different smaller study in 280 women in Italy reported lower rates of CVR discontinuation over a 1-year period than two types of COCs [51]. In this study, discontinuation rates were 22.3% for women taking pills containing 20 mcg EE/100 mcg LNG, 30.4% for those taking pills containing 15 mcg EE/60 mcg gestodene, and 11.7% for those using the ENG/EE ring.

Patient Compliance

In the initial noncomparative studies of the ENG/EE ring in Europe and North America mentioned above, CVR compliance ranged from 80% to 90% and was higher in Europe [16, 17, 32]. Prolonged or shortened ring-free periods occurred in less than 5% of the cycles; 1–2% of women left the ring outside the vagina greater than the recommended 3 hours. Two other large studies comparing CVR and COC use report high (>85%) rates of compliance for both COCs and the CVR [19, 20]. In a crossover study comparing CVR and COC use among adolescents, compliance was similar, although adolescents reported that the CVR was easier to remember to use correctly than COCs [52].

A Spanish cross-sectional multicenter study including 26,250 typical users of CHCs reported that noncompliance, including missed or delayed pill doses, patch application, or ring insertion, was significantly lower in women who used the CVR (22%) compared to those who used COCs (71%) or the patch (32%) [53]. Emergency contraception was requested by 6% of women who used the CVR compared to 14% of COC users and 11% of patch users.

Bleeding Pattern

The bleeding profile with the ENG/EE ring is highly predictable due to sustained low-dose release and absorption of EE throughout the cycle. Withdrawal bleeding usually occurs within 2–3 days of ring removal and may continue beyond the 7-day

ring-free period. Expected bleeding during the ring-free interval occurred in 98.5% of women in a large study of 2,322 women over 13 cycles [17]. Median onset of bleeding was on day 3 after ring removal, and mean duration of bleeding was 4.5–5.2 days. Irregular or breakthrough bleeding occurred in 6% of cycles. Early withdrawal bleeding (i.e., onset of bleeding just prior to ring removal for the ring-free interval) occurred in 6% of cycles, and late withdrawal bleeding (i.e., bleeding past the 7-day ring-free interval) occurred in 24% of cycles.

CVR users have less breakthrough bleeding or spotting with the recommended 28-day cycle, especially in the first few months of use, compared to users of both monophasic and triphasic COCs [20, 51, 54]. In a randomized controlled trial including 1,030 women comparing cycle control between the CVR and a COC containing 30 mcg EE/150 mcg LNG, the incidence of breakthrough bleeding and spotting over cycles 2–13 was lower with the CVR (range 2.0–6.4%) than with COCs (range 3.5–12.6%), which reached significance for cycles 2–9. The incidence of intended bleeding was significantly higher in the CVR users (59–73%) compared with COC users (43–58%).

Extended CVR regimens result in decreased total bleeding days per year but an increase in unscheduled bleeding/spotting days. With extended regimens, unscheduled bleeding is more frequent than with the standard 28-day cycle. A one-year open-label study across ten European and ten American centers studied four regimens of CVR use: a 28-day cycle (21 days with ring in place followed by 7 ring-free days), a 49-day cycle (42 days with ring in place followed by 7 ring-free days), a 91-day cycle (84 days with ring in place followed by 7 ring-free days), and a 364-day cycle (357 days with ring in place followed by 7-day ring-free interval) [55]. The percent of days with either bleeding or spotting increased stepwise from 18% in the 28-day cycle to 24% in the 364-day cycle.

Compared to extended COC regimens, total and unscheduled bleeding days decrease with the CVR, while scheduled bleeding days increase. In a study comparing extended CVR and COC regimens (84 days of use of either the CVR or COCs followed by 7-day pause during one year), the mean total number of bleeding days decreased significantly during the one-year period with both methods ($p < 0.01$). CVR users had more days of scheduled bleeding than COCs (16.3 days with CVR vs. 14.2 days with COCs, $p < 0.01$). Both groups had less unscheduled bleeding and spotting ($p < 0.01$); however, CVR users had less than COC users (21.7 days with CVR vs. 22.9 days with COCs, $p < 0.01$). The conclusion of the study was that extended vaginal ring regimen is a contraceptive method that offers good cycle control [56].

Patient Selection

Prior to initiation of the CVR, women should be counseled on alternative methods of contraception, including other combined hormonal methods and LARCs. Advantages and disadvantages of CVR use, as well as the potential risks and side effects, should be reviewed thoroughly and documented. Women should be screened

for contraindications to the CVR (see below) and have their blood pressure checked. Recommended well-woman care can be performed in conjunction when clinically indicated, including STI screening and routine cervical cancer screening.

Advantages of the CVR

- Once-a-month dosing schedule that does not require daily patient compliance.
- User-control over initiation and discontinuation.
- Discrete method that is not visible like the patch and does not require packaging such as COCs.
- Noncontraceptive benefits:
  - Cycle control is improved compared to many COCs.
  - Highly dependable bleeding pattern with reduced monthly bleeding.
  - Reduced dysmenorrhea.
  - Reduced acne and androgen-associated symptoms.
  - Improvement in endometriosis symptoms [57].
  - Decreased risk of endometrial and ovarian cancers.
  - Less impact on insulin resistance than COCs [58].

Disadvantages of the CVR

- Ring-related problems: expulsion, pain, or discomfort
- Increased vaginal secretions
- No protection against STIs
- Cost: $0–$200 depending on insurance and pharmacy, no generic available

Poor Candidates

Women who may benefit from an alternate form of contraception and are not ideal candidates for the CVR include those with the following:

- Emotional or physical discomfort with or inability to insert the ring vaginally (musculoskeletal problems, poor functional status, or personal preference)
- Pelvic organ prolapse or other pelvic floor disorders
- Contraindications to estrogen or progestins

Contraindications

CHCs including COCs, the CVR, and the contraceptive patch are safe for the majority of women of reproductive age. Certain contraindications apply to all CHCs, including the CVR. Women with these conditions should be individually counseled on their available contraceptive options, weighing the risks of a contraceptive method against those of unplanned pregnancy. Very important red flags to closely evaluate for are the presence of hypertension, migraines, and/or tobacco smoking. Relative and absolute contraindications, according to the Centers for Disease Control and Prevention's Medical Eligibility Criteria for Contraceptive Use, are listed in Table 5.1.

Table 5.1 Centers for Disease Control and Prevention: United States Medical Eligibility Criteria for Contraceptive Use, 2016 – combined hormonal contraceptives (including the CVR) [59]

Category 3 – Proven or theoretical risks usually outweigh benefits	Category 4 – Unacceptable risk if contraceptive method is used
Breastfeeding and <1 month postpartum Postpartum <21 days Smoking (0–15 cigarettes per day) and >age 35 Hypertension History of DVT/PE with no risk factors for recurrence History of peripartum cardiomyopathy (>6 months prior) with normal or mildly impaired cardiac function History of breast cancer with no evidence of disease for >5 years Diabetes with nephropathy/retinopathy/neuropathy or other associated vascular disease Active, symptomatic gallbladder disease History of COC-related cholestasis Current use of ritonavir-boosted protease inhibitors for antiretroviral therapy, certain anticonvulsants, or rifampicin or rifabutin therapy (see medication interactions)	Peripartum cardiomyopathy within 6 months Moderate or severely impaired cardiac function (New York Heart Association Functional Class III or IV) Solid-organ transplant complicated by failure, rejection, or vasculopathy Smoking 15 or more cigarettes per day and age ≥35 Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension) Severe hypertension Vascular disease History of deep venous thrombosis or pulmonary embolism (DVT/PE) with risk factors for recurrence Acute DVT/PE Major surgery with prolonged immobilization Known thrombogenic mutations Current or past ischemic heart disease or stroke Complicated valvular heart disease (pulmonary hypertension and history of bacterial endocarditis) Systemic lupus erythematosus with positive antiphospholipid antibodies Migraine with aura, or any migraine over age 35 Current breast cancer Severe/decompensated liver cirrhosis Hepatocellular adenoma or malignant hepatoma

Adverse Effects

Ring-Related Problems

Up to 2–6% of CVR users experience ring-related problems, including discomfort, expulsion of the ring, or issues during intercourse [17]. Ring expulsion can occur in as many as 20% of women during the 3-week cycle of use [47]. This usually occurs at the time of Valsalva with defecation or strenuous activity, intercourse, or tampon removal. Very rarely, the contraceptive ring may break at the weld joint, which does not impact the contraceptive effectiveness, but may make the ring more likely to slip

out [33]. In the event of a broken ring, the broken ring should be removed and new ring inserted. Impact of CVR use on sexual intercourse is discussed later in this chapter.

Vaginal Symptoms

Incidence of vaginal symptoms with the CVR is higher than with other CHCs. In large studies, 6% of women reported vaginitis and 5% reported leukorrhea [16, 17]. In a Cochrane meta-analysis comparing the CVR with the patch and COCs, both vaginitis and leukorrhea were more likely with the CVR (vaginitis OR 2.48–2.84 and leukorrhea OR 3.21–6.42).

All CVRs, even placebo rings, are associated with an increase in vaginal secretions when compared with COCs or to no contraception [12]. This is thought to be secondary to a weak local inflammatory response that increases secretions but does not significantly alter the vaginal flora or cause infection. Two clinical trials studied the effects of the ENG/EE ring on vaginal flora during 6 months of use compared to COC users [60, 61]. In these trials, there was no change in colony counts of vaginal aerobes, anaerobes, *Candida*, lactobacilli, *Gardnerella vaginalis*, or *Neisseria gonorrhoeae* when compared to colony counts before ring insertion or compared to COC users. Vaginal cytology was also not different, with the exception of an increase in leukocytes. Bacterial vaginosis was not more common in CVR users [47]. Finally, the CVR is not associated with an increase in cervical or vaginal dysplasia [60].

Hormonal Effects

The ENG/EE ring is associated with similar systemic side effects as low-dose COCs. Given lower circulating levels of EE with the ENG/EE ring, incidence of these side effects has been reported to be similar or lower compared to COCs [19, 20]. The most frequent side effects cited by women in large trials include the following:

- Headache (5.8%)
- Subjective weight gain (4.0%)
- Nausea (3.2%)
- Emotional lability (2.8%)
- Breast tenderness (2.6%)
- Dysmenorrhea (2.6%)

Venous Thromboembolism

The use of low-dose COCs has been shown to increase the risk of venous thromboembolism (VTE) three- to four-fold (12–20 per 100,000) above baseline risk (4–5 per 100,000) [62]. EE affects hepatic synthesis of coagulation factors, leading to changes in the procoagulant, anticoagulant, and fibrinolytic pathways that increase the risk of VTE. Favorable factors with the CVR with regard to VTE risk include vaginal absorption and bypass of the first-pass hepatic metabolism of EE as well as lower circulating levels of EE. However, ENG, a third-generation progestin, has been associated with a two-fold higher risk of VTE as compared to second-generation progestins such as LNG in several studies as discussed below [63].

Several large retrospective cohort studies have addressed the risk of VTE from CHCs, including the CVR. In 2011, the FDA published an analysis of US insurance claims data including 835,826 women and reported a relative risk of VTE of 1.56 (95% CI 1.02–2.37) in CVR users compared to COC users [64]. However, in secondary analyses adjusting for duration of use, the CVR was not associated with higher risk of VTE compared to COCs. In another large Danish registry-based cohort study, the relative risk of VTE in CVR users was 1.9 (95% CI 1.3–2.7) compared with users of LNG-containing COCs and 6.5 (95% CI 4.7–8.9) compared to nonusers of hormonal contraception [62]. Finally, the Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring (TASC) study is the only prospective cohort study addressing this topic and included over 66,489 woman-years of CVR use [37]. This study estimated an incidence of VTE of 8.3 and 9.2 per 10,000 woman-years for the CVR and COCs, respectively. The adjusted hazard ratio for VTE in CVR users compared to COC users was 0.8 (95% CI 0.5–1.5). The incidence of arterial thromboembolism (ATE) in CVR users was 2.2 per 10,000 woman-years (95% CI 0.7–5.1), with a hazard ratio for the CVR compared to COCs of 0.7 (95% CI 0.2–2.3).

In summary, most of the evidence supports a small increased risk of VTE with ENG/EE ring use similar to that of COCs. These data must be interpreted taking into account the fact that the absolute risk of VTE with hormonal contraception (including the CVR) is still low and much lower than that in pregnancy or postpartum.

Weight Gain

Most women do not experience weight gain while using the ENG/EE ring, and those that do gain weight usually gain only a small amount, which is comparable to COCs. The initial noncomparative European and American data showed a mean body weight increase of 0.84 ± 3.81 kg over 13 cycles [16, 17]. Another randomized

trial that compared weight gain between the CVR and COCs over a 3-month period found that participants gained an average of 2.8 lbs with either method; thus, this was not significantly different between the groups [65]. Weight gain also does not appear to vary by baseline BMI.

Hyperlipidemia

For normal weight women without baseline hyperlipidemia, the ENG/EE ring when used as recommended in a 28-day cycle has a neutral effect on lipid profiles, with no significant change in total cholesterol, LDL, HDL, or triglycerides over 1 year of use [66]. Extended-use ENG/EE ring regimens were found to have small but significant increases in total cholesterol, HDL, and triglyceride levels in a prospective cohort study [67]. Further research is needed on changes in lipid profiles in women with hyperlipidemia.

Mood Changes

Data on mood changes and depression with the ENG/EE ring are mixed. Generally, the incidence of negative mood symptoms is reduced in CVR users compared to COC users. In a prospective study of 280 women, irritability and depression were experienced by significantly fewer ring users (4% and 4%, respectively) compared with women taking COCs containing either LNG/EE (16% and 9%, respectively) or gestodene/EE (11% and 9%, respectively) after three cycles. Another study reported that women who initiated the ENG/EE ring were less likely to report changes in their mood, whereas those who initiated COCs were more likely to report a negative change in mood [68].

Sexual Function

In a study evaluating the impact of the ENG/EE ring on sexual function, 89% of women and 68% of partners never felt the ring during intercourse, 10% of women and 24% of partners felt it occasionally, and 1% of women and 8% of partners always felt it [69]. Studies report that 13–16% of women choose to remove the ring during intercourse, which does not affect efficacy if replaced within 3 hours with the ENG/EE ring and within 2 hours for the SA/EE ring [39, 47].

Studies also suggest that psychosexual function may be improved with the CVR. In a study comparing the ENG/EE ring to two types of COCs, sexual desire and satisfaction were increased in the majority of CVR users over 3–12 cycles of use, whereas sexual desire and satisfaction were decreased to unchanged over the

same time period in COC users [51]. Another study similarly found improved markers of sexual function in women using either COCs or the CVR. This study also highlighted an increase in sexual fantasy among CVR users [69].

Drug Interactions

As described above, CVR efficacy is not altered by simultaneous use of tampons, nonoxynol-9 spermicide, or miconazole vaginal suppositories, and all these products can be used without compromising the efficacy of the CVR or the other vaginal product [42–46].

Some drugs can interfere clinically with the action of COCs by inducing liver enzymes that convert the steroids to less biologically active metabolites, thus lowering their contraceptive effect [59]. These interactions are expected to be similar for the CVR, although most have not been directly studied. Drugs that may reduce the efficacy of the CVR include the following:

- Anticonvulsants: phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine
- Certain antimicrobials: rifampicin or rifabutin
- Antiretroviral ritonavir-boosted protease inhibitors and some nonnucleoside reverse transcriptase inhibitors

Progestin-Only Rings

As described previously, progestin-only rings were the first CVRs developed and studied. The mechanism of action of progestin-only rings is largely due to thickening of cervical mucus to prevent sperm penetration. They also inhibit ovulation, albeit to a lesser degree than when combined with estrogen, and reduce endometrial receptivity [26, 70]. Progestin-only rings have advantages of a longer duration of wear and can be used in women in whom estrogen is contraindicated. They also are particularly well suited for use in postpartum or lactating women given they prolong lactational amenorrhea and do not decrease milk supply. Hormone levels transferred to the infant are also essentially negligible.

Unfortunately, the use of progestin-only rings has largely been replaced by the combined ring in the majority of countries, with the exception of a single progesterone-containing ring, the Progering, which is commercially available only in South America for lactating women [71]. The Progering (Laboratorios Silesia, Santiago, Chile) releases 10 mg of progesterone daily and is designed for continuous use over 4 months [70, 72]. It is doughnut-shaped and composed of soft, flexible silicone elastomers and micronized progesterone, with an overall diameter of 58 mm [73]. Though use is not widespread at present, progesterone vaginal rings

are a promising contraceptive option for postpartum women that could have benefits in promoting both lactation and pregnancy spacing.

Future Directions

The next decade is sure to bring exciting innovations in multipurpose vaginal ring technology with advances in both contraception and prevention of HIV/AIDS and STIs. Firstly, arrival of the SA/EE ring to the contraceptive market within the next year will have exciting implications for family planning and global health. Another CVR including SA, similar to the SA/EE ring but with estradiol (E2) instead of EE, is also under investigation [23]. E2 does not appear to increase the risk of thrombosis when studied in postmenopausal women for hormone replacement therapy, and thus the use of E2 instead of EE could improve the safety profile of the CVR with regard to VTE risk. Selective progesterone receptor modulators, in particular ulipristal acetate, also are under study for administration via a 3-month vaginal ring [74]. Primary results have yielded very promising anovulation rates; however, the effects of ulipristal acetate on endometrial thickening require continued investigation [74].

Several vaginal rings for use in HIV/AIDS prevention are currently in development and have exciting applications in pre-exposure prophylaxis for women worldwide. A dapivirine vaginal ring was developed by the nonprofit International Partnership for Microbicides (IPM) and was found in two large-scale phase III trials, both The Ring Study and ASPIRE, to reduce HIV-1 transmission by about 30% [75, 76]. In two subsequent open-label studies, DREAM and HOPE, HIV risk seems to be even further reduced to approximately 50–60% with increased utilization of the dapivirine ring [77]. Dapivirine in combination with LNG is also under study for combined HIV prevention and contraception by IPM. A phase I study has also been completed evaluating a vaginal ring containing a combination of tenofovir and LNG [78].

Conclusion

The ENG/EE ring is a highly effective method of contraception with similar efficacy to COCs and the patch when used in routine cyclic or extended regimens and offers a favorable side effect profile. It is easy to use, discrete, and user-controlled, all of which lead to high patient satisfaction. Serum concentrations of hormones rapidly reach a steady state, without the daily fluctuations of COCs and are lower than oral or transdermal delivery. The bleeding profile is highly predictable, and cycle control is excellent. CVRs are also an area of active research and development, with exciting applications in family planning, infectious disease, and global health.

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Chapter 6
Depot Medroxyprogesterone Acetate

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General Overview of Method

Depot medroxyprogesterone acetate (DMPA) is an injectable progestin-only contraceptive administered every 13 weeks. Users of DMPA can be up to 2 weeks late for their repeat injection without requiring additional contraceptive protection or pregnancy testing before reinjection [1].

DMPA is an extremely effective contraceptive agent when used perfectly. With typical use, approximately 6 out of 100 women will become pregnant in the first year of use, reflecting that some users do not return for repeat injections [2]. DMPA is reversible and can be used by women of all ages, from adolescence until menopause [3]. Unlike other hormonal contraceptive methods, there is a delayed return to fertility after discontinuation (median duration 10 months after the last injection) [4, 5].

With typical use, failure rates are higher with DMPA than intrauterine devices (IUDs) or contraceptive implants. Nonetheless, in many settings, women who do not have access to IUDs/implants or prefer not to use these methods choose DMPA either for its convenience, privacy, or because it represents a progestin-only contraceptive option.

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Category Options

Since its introduction into the market in the 1960s as Depo-Provera®, DMPA has been used to treat a variety of gynecological conditions including endometriosis and abnormal uterine bleeding. For many years, DMPA was also commonly used "off-label" as a contraceptive agent, especially in women who were not candidates for combined oral contraceptives (COCs). In 1992, the Food and Drug Administration (FDA) approved the marketing of DMPA as a contraceptive agent. Depo-Provera and generic formulations are available in 1-mL injection vials containing 150 mg of medroxyprogesterone acetate (MPA) as a sterile, white, injectable suspension. It should be stored at room temperature (15–30 °C). Just before injection, the vial should be vigorously shaken so that a uniform suspension is administered. It is administered by deep intramuscular injection into the gluteal or deltoid muscles.

In December 2004, depo-subQ provera 104™ (depo-subQ), a newly formulated medroxyprogesterone acetate, was approved by the FDA as a new contraceptive option. Subsequently, depo-subQ received approval from the FDA as a treatment of endometriosis-related pain. Depo-subQ is given subcutaneously and uses a much smaller needle than DMPA. Depo-subQ is available in prefilled syringes, each containing 0.65 mL (104 mg) of MPA sterile aqueous suspension for subcutaneous injection. Subcutaneous injections can be given in the anterior thigh or abdominal wall. Depo-subQ has an efficacy and side effect profile similar to DMPA [6]. However, subcutaneous injections are less painful and may potentially be given by self-injection. Depo-subQ is also FDA-approved for the treatment of endometriosis.

Clinical Effectiveness

In a large World Health Organization (WHO) clinical trial, the 1-year pregnancy rate with use of DMPA was only 0.1% and the 2-year cumulative rate was only 0.4% [7]. With perfect use, the failure rate is 0.2%, whereas typical use failure rate is 6% [2]. Adjusting the dose for weight is not necessary. When depo-subQ was administered for contraception in a clinical trial, no pregnancies were detected among 2042 women using depo-subQ for up to 1 year [6].

For the treatment of endometriosis, depo-subQ given every 3 months was statistically equivalent to leuprolide given every 3 months across all endometriosis-associated pain categories (i.e., pelvic pain, pelvic tenderness, painful periods, painful intercourse, and hardening/thickening of tissues) in an 18-month study [8].

Mechanism of Action

MPA is a 17-acetoxy-6-methyl progestin that has progestogenic activity in humans [4]. There are three mechanisms of action that contribute to injectable MPA's contraceptive efficacy.

- Ovulation: suppression of the hypothalamus and secretion of gonadotropins, which in turn prevents follicular maturation and ovulation; this is DMPA's major mechanism of action [9].
- Cervical mucus: making it viscous, thick, and scanty, thus preventing sperm penetration; sperm are unlikely to reach the oviduct and fertilize an egg.
- Endometrium: becomes thin and atrophic [10].
  - Endometrium does not secrete sufficient glycogen to provide nutrition for a blastocyst entering the endometrial cavity.

Suppression of estradiol concentrations and a possible direct action of injectable MPA on lesions of endometriosis (causing thinning and atrophy) are likely responsible for the therapeutic effect on endometriosis-associated pain.

Picking the Right Candidate

Good Candidates

- Women who find daily, weekly, monthly, or "at the time of intercourse" contraceptive options difficult to use
- Women who cannot use estrogen-containing contraceptives
- Women who need convenient short-term contraception, such as those getting a rubella vaccination, awaiting tubal sterilization, using teratogenic medications such as isotretinoin, or immediately following a hysteroscopic tubal occlusion procedure or male partner vasectomy
- Women with special needs in managing menstrual hygiene (e.g., cognitive impairment, military personnel, those who are wheelchair-bound, and athletes)
- Women with heavy menstrual bleeding [11]
- Women with endometriosis-related pain or dysmenorrhea [8]
- Obesity (≥30 body mass index)
  - DMPA is generally safe and effective for obese women, although further weight gain is a concern and should be monitored
- Women with sickle cell disease [12]
- Women with epilepsy [13]

Poor Candidates

- Women who do not have access to injections every 3 months
- Women who would like to conceive a pregnancy in the short term
- Women who cannot accept changes to their menstrual bleeding pattern
- Women with current breast cancer

Advantages

Contraceptive-Linked Benefits

- Dosing once every 3 months
- Highly effective method regardless of weight
- Private
- Minimal drug interactions

Non-contraceptive Benefits

- Decreased menstrual blood loss
  - Decreased risk of anemia
  - Amenorrhea is an advantage to many users

    50% of users are amenorrheic at 1 year of use [14]
    70% are amenorrheic after 2 years of use

  - Treatment of abnormal uterine bleeding associated with uterine fibroids, adenomyosis, or coagulopathies [15]
- Decreased dysmenorrhea
- Decreased cyclical menstrual symptoms such as mood changes, headaches, and breast tenderness
- Decreased risk of endometrial and ovarian cancer [16, 17]
- Decreased risk of pelvic inflammatory disease
- Decreased risk of ectopic pregnancy
- Fewer sickle cell crises in women with sickle cell disease
- Decreased frequency of grand mal seizures in women with epilepsy
- Treatment of pain associated with endometriosis

Disadvantages

- Cannot be discontinued immediately
- Delay in return to fertility
- Some users experience weight gain

Side Effects

- Bleeding abnormalities
  - Unpredictable, irregular, or frequent bleeding
  - Amenorrhea (if undesired)
  - Bleeding-related side effects lead to discontinuation rates of 25% to 50% in the first year of use [18, 19].
- Weight gain
  - High-dose progestin therapy may increase appetite and therefore weight, but the impact of DMPA on weight is controversial.
  - A 2016 systematic review concluded that the average weight gain with DMPA use is approximately 2 kg; however, there is marked individual variation [20].
  - A randomized controlled trial failed to show that DMPA causes weight gain [21].
  - A prospective cohort study found that compared to nonblack women, African-American women gained more weight with use of various hormonal contraceptives (including DMPA) [22].
  - For the individual patient, excessive weight gain should prompt consideration of an alternative method of contraception.
- Breast tenderness
- Headache
- Mood changes
  - Depression is not a contraindication to DMPA use [23].
- Nausea
- Acne
- Pain at injection site
- Hypoestrogenic effects, hot flashes, and vaginal dryness
- Reversible decreases in bone mineral density

Serious Side Effects

- Allergic reactions (rare)

Warning Signals

- Persistent, severe headaches
- Unusually prolonged, heavy vaginal bleeding
- Worsened depression
- Symptoms or signs of pregnancy
- Pain, redness, pus, or bleeding at injection site

- Allergic reaction (difficulty breathing, tightness of throat, hives, or swelling of lip, tongue, or face) (rare)

Reproductive Effects

- Within 10 months of the last injection, half of women who discontinue DMPA to become pregnant will conceive [24].
- In some women, fertility will not return until 18 months after the last injection.
- Before initiating DMPA contraception, women should understand the possible prolonged duration of contraceptive action.
- Women who may want to become pregnant within the next year should choose an alternative contraceptive.
- Pregnancy rates 1 year after the last DMPA injection are similar to rates in non-users, indicating that there are no long-term effects on fertility from past use [24].

Drug Interactions

- The only medication that may decrease the effectiveness of DMPA is aminoglutethimide, an infrequently prescribed drug used to suppress adrenal function in some women with Cushing's Disease.
- There are no known interactions between DMPA and the following classes of medications:
  - Antiretroviral therapy
  - Antiepileptic medications
  - Antibiotics
  - Selective serotonin reuptake inhibitor (SSRI) and Serotonin-norepinephrine reuptake inhibitor (SNRI) medications

Special Issues

Postpartum

DMPA may be used immediately postpartum in women who are not breastfeeding (USMEC category 1).

For breastfeeding women who are considering DMPA for postpartum contraception, there is theoretic concern that initiating progestin contraception immediately after birth could prevent lactogenesis since progesterone withdrawal after placental delivery is thought to trigger prolactin secretion [25]. However, observational studies of progestin-only contraceptives suggest that there is no detrimental effect on successful initiation and continuation of breastfeeding or on infant health, growth, and development when progestin-only contraceptives are used less than 6 weeks postpartum [26, 27].

There is general consensus that progestin use after the onset of lactogenesis (typically in the first 48–72 hours postpartum) does not affect breastfeeding performance. As such, the benefits of DMPA generally outweigh the risks in the first 30 days postpartum for breastfeeding women (USMEC category 2) and there is no restriction on the use of DMPA for breastfeeding women who are 30–42 days postpartum (USMEC category 1) [25].

Skeletal Health

Conditions that affect sex hormones (e.g., pregnancy, breastfeeding, menopause, and use of hormonal contraceptives) can impact bone mineral density (BMD) [28]. DMPA reduces the secretion of pituitary gonadotropins, thereby decreasing ovarian production of estrogen and a resulting decline in BMD. In 2004, the FDA added a "black box" warning to DMPA labeling about declines in BMD [29], which might discourage women and health care providers from initiating DMPA or limit long-term use.

However, given that this warning is not evidence-based, guidance from professional organizations including ACOG and CDC does not support limiting duration of DMPA use [30, 31].

Both DMPA use and breastfeeding represent hypoestrogenic states. The reversible decline in BMD associated with DMPA use, followed by recovery when the hypoestrogenic state is reversed, parallels the BMD trends seen with breastfeeding [32, 33]. Cross-sectional studies have demonstrated that BMD in former adult DMPA users is similar to that of never users, providing reassurance that loss of BMD associated with DMPA use is likely reversible [30].

Cross-sectional and longitudinal studies evaluating women aged 18–54 years demonstrate lower BMD in current DMPA users compared with nonusers [30, 34]. However, recovery of BMD occurs after discontinuation of DMPA. In trials that included both adults and adolescents, with a duration of DMPA use of 2–5 years and follow-up of up to 5 years after discontinuation, losses in BMD appeared to be substantially or fully reversible [30, 35]. Clinicians should be mindful that decline in BMD associated with DMPA use is nonlinear, with BMD decline being greatest in the first 2 years after initiation and subsequently plateaus. Furthermore, use of DMPA among adolescents does not impact achievement of peak bone mass.

In a multicenter, prospective, study of adolescents who initiated and continued DMPA injections for up to 240 weeks, BMD was assessed at baseline, during use, and for up to 300 weeks after DMPA cessation. At conclusion of DMPA use, mean BMD had declined 2.7% (lumbar spine) and 4.1% (total hip) from baseline. Within 60 weeks of DMPA discontinuation, mean lumbar spine BMD had returned to baseline levels and subsequently increased 4.7% *above* baseline 240 weeks after DMPA discontinuation. Mean total hip values recovered toward baseline more slowly [36].

BMD changes associated with DMPA are of clinical concern if they elevate risk for fracture. The association between BMD and risk of fracture has been best

studied in postmenopausal women, a population in which BMD predicts fracture risk [28]. In contrast, because fracture risk is so low, the relationship between BMD and fracture risk is weak in healthy premenopausal women, and differences in BMD are associated with very small differences in absolute fracture risk [37]. If declines in BMD caused by use of DMPA increase fracture risk, this association would most be noticeable in postmenopausal women. No published data address whether contraceptive use of DMPA impacts fracture risk in postmenopausal women. However, observational findings are mixed regarding the association of DMPA use and fracture risk in reproductive age women, a population in which fractures are not likely to result from low BMD.

Three studies relied on large national datasets to examine the association between fracture and DMPA or levonorgestrel (LNG)-IUD use [38–40]. Two of these were based on the same large UK database [38, 39]. The first, a case–control study, noted a higher risk of fracture associated with ever use of DMPA compared with never use (OR, 1.44) [38]. Using the same UK database, a second publication employed a retrospective cohort analysis and also observed that DMPA users had an increased risk for fracture (OR, 1.41). However, this latter report noted that the elevated risk was present at baseline, *prior* to DMPA use, and therefore could not have been caused by DMPA [39]. A case–control study from Denmark also found that ever use of DMPA was associated with increased risk for fracture (OR 1.44), but suggested that the subgroup of women choosing DMPA (0.1% of the study sample) was not representative of the larger Danish population, thereby limiting the interpretation of results [40]. The authors of both the UK and the Danish studies suggest that women who choose DMPA are behaviorally different from women who choose other methods of contraception and speculate that fracture risk associated with DMPA exposure may in fact be due to unmeasured confounders in women who choose injectable contraception. For example, in the Danish study, the prevalence of alcohol abuse (which is associated with fractures from motor vehicle and other accidents) in women using DMPA was 14%, seven-fold higher than in women not using DMPA, and cases with fractures were three-fold more likely to be classified as alcoholics as compared to control women.

Counseling and Management Considerations

Clinicians should counsel women and adolescents considering initiating or continuing DMPA about the benefits and the risks of DMPA and should discuss the FDA "black box" warning, using clinical judgment and shared decision making to assess appropriateness of use.

Guidance from professional organizations including ACOG and CDC indicate that the effect of DMPA on BMD and potential fracture risk should not prevent practitioners from prescribing DMPA or continuing use beyond 2 years [30, 31, 41]. (USMEC category 2 for adolescents <18 years of age and women >45 years of age; USMEC category 1 for women age 18–45 years).

Routine BMD monitoring is not recommended in adolescents and young women using DMPA, regardless of duration of use. Although studies of adolescents and women demonstrate that low-dose estrogen supplementation limits BMD loss in DMPA users [30], estrogen supplementation during DMPA use is not recommended because of potential adverse effects and lack of evidence from clinical trials assessing skeletal health outcomes.

Individualized care and counseling is recommended for women with comorbidities that may influence bone health, including disabilities that increase risk of falls or involve being wheelchair bound, chronic corticosteroid use, renal disease, or malabsorption.

> Regular exercise (including weight-bearing exercise), smoking cessation, and age-appropriate calcium and vitamin D intake should be encouraged for all women.

Adolescents should be counseled about other contraceptive methods and offered the option of initiating or transitioning to long-acting reversible contraceptive methods that have no effect on BMD, such as intrauterine devices and contraceptive implants, as alternatives to long-term DMPA use.

Professional organizations advise that the advantages of DMPA use as a contraceptive outweigh the theoretical concerns regarding skeletal harm [30, 31, 42]. Concerns about skeletal health should not restrict initiation or continuation of DMPA in reproductive age women, including teens and women older than 35 years [41].

Sexually Transmitted Infection Risk

Risk of STI Acquisition

DMPA, similar to all hormonal contraceptives, does not protect users from acquiring sexually transmitted infections (STIs). Consistent condom use continues to be recommended for protection against STIs such as gonorrhea, chlamydia, and HIV. There is inconsistent and often conflicting data regarding DMPA use and the risk of STI acquisition.

> Multiple studies have looked at STI rates among hormonal contraceptive users with mixed results and often with important methodological shortcomings. Some studies of DMPA users demonstrate an increased rate of gonorrheal and chlamydial infections, but a decreased rate of trichomoniasis infections and pelvic inflammatory disease when compared to oral contraceptives [43].

DMPA is popular among women served by rural health care workers and international organizations due to its convenience, low cost, ease of use, and prolonged duration of action. Effective contraception is critical in areas of high HIV prevalence to decrease or prevent vertical transmission. Previous studies have suggested that DMPA may actually lead to an increase in transmission of the HIV virus [44, 45].

Primate studies have suggested that transmission of simian immunodeficiency virus (SIV) is significantly increased with the use of DMPA. In these studies, the use of DMPA resulted in marked vaginal mucosal thinning, hyperplasia of cervical columnar cells, and cervical ectopy, thereby increasing the risk of acquisition of SIV [46, 47]. However, these findings were not noted in several small human studies [48–50]. Furthermore, DMPA and other progestins have been shown to thicken cervical mucus, thus decreasing the risk of ascending infections.

DPMA acts upon glucocorticoid receptors, exerting a glucocorticoid effect of suppression of T-cell-mediated defense, theoretically increasing the risk of acquisition of HIV [51]. However, the clinical importance of this has yet to be determined.

WHO and the CDC continue to recommend DMPA use for all women, including those at risk for and living with HIV. DMPA remains category 2 in the revised USMEC for women at high risk for HIV, stating that the "advantages of progestin-only injectable contraceptive use (including DMPA) by women at high risk for HIV infection outweigh the theoretical or proven risks." [31, 52].

Furthermore, prior studies on HIV acquisition with the use of DMPA suffer from methodologic limitations that prevent these studies from guiding clinical decisions [53]. Fortunately, two recent studies including a large WHO randomized trial did not show an increased rate of STIs when accounting for sexual habits amongst DMPA and non-DMPA users [53, 54]. Accordingly, patients should be counseled that DMPA will not increase their risk of HIV, and women should not be denied access to DMPA due to a concern for HIV acquisition.

Women who are currently living with HIV can continue to use DMPA (USMEC category 1) as it is well tolerated, easy to access, and there has been no evidence of DMPA interference with any existing antiretroviral therapies [31, 53].

Cardiovascular Risk

DMPA use reduces high-density lipoprotein (HDL) levels, a finding of uncertain clinical significance, but does not increase production of coagulation factors and has no adverse effect on blood pressure. DMPA use is not associated with increased risk of myocardial infarction or stroke in healthy women. No adverse clinical effects on cardiovascular disease have been observed [11].

Current MEC from the Centers for Disease control indicates that DMPA and other progestin-only contraceptives can be used by women with a history of venous thromboembolism (VTE) and those in whom use of combination (estrogen–progestin) contraception is contraindicated [3]. This recommendation differs from package labeling for DMPA (written in the 1960s), which indicates that a prior history of VTE is a contraindication to DMPA use.

A systematic review by Tepper et al. in 2016 included 26 studies examining thrombosis among women utilizing progesterone-only contraception and found limited evidence suggesting an increased odds risk of VTE with the use of injectable progestin-only contraceptives. However, many of these studies were of low power or poor quality. In women with multiple risk factors for cardiovascular disease (e.g., smoking, older age, hypertension, diabetes), the risks of using DMPA may outweigh the benefits. The basis for this caution relates to hypothetical concerns regarding the hypoestrogenic effects of DMPA and reduced HDL levels [3]. In addition, the effects of DMPA might persist for some time after discontinuation so it would not be immediately reversible if there were an adverse event.

Women who are immediately postpartum often initiate DMPA contraception due to its ease of access, ability to administer while still in the hospital, compatibility with breastfeeding, and duration of effect. However, postpartum women are at an elevated risk of VTE compared with nonpregnant women. A recent study found use of DMPA within the first 7 days postpartum noted an increased incidence of VTE compared to nonuse of hormonal contraceptives [55]. The absolute incidence of VTE, however, was low (0.42/10,000). In this observational study, the women who utilized DMPA within the first 7 days postpartum may have had a higher prevalence of comorbidities that increased their overall risk of VTE regardless of contraceptive use. Accordingly, further studies are needed to make definitive recommendations. One must also balance the overall low incidence of VTE with the risks associated with unintended short interval pregnancies.

Cancer Risk

Use of DMPA is associated with either decreased or negligible change in cancer risk. Ever users of DMPA have a 80% decrease in endometrial cancer risk compared to never users, which is similar to the protective effect associated with the use of combined oral contraceptives [56]. Ever use of DMPA is also associated with a 39% decrease in ovarian cancer risk, with an 83% decrease after 3 years of use [17]. There is no impact of DMPA use on cervical cancer risk [57]. Although two small studies have suggested that recent DMPA use may elevate the risk of breast cancer, most studies have found no association between DMPA use and risk of breast cancer [58–60].

Contraindications

Contraindications to DMPA are few. The 2016 U.S. Medical Eligibility Criteria for Contraceptive Use (USMEC) from the CDC were adapted from the World Health Organization's Medical Eligibility Criteria for Contraceptive Use, fourth edition [3]. These guidelines provide evidence-based advice on the safety of contraceptives.

Relative (USMEC Category 3 – A Condition for Which the Theoretical or Proven Risks Usually Outweigh the Advantages of Using the Method)

- Multiple risk factors for arterial cardiovascular disease (including older age, smoking, diabetes, hypertension, and hyperlipidemia)
- Severe hypertension (systolic ≥160 mm Hg or diastolic ≥100 mm Hg)
- Hypertension with vascular disease
- Current or personal history of ischemic heart disease
- Stroke (history of cerebrovascular accident)
- Systemic lupus erythematosus (SLE) with positive (or unknown) anti-phospholipid antibodies
- SLE with severe thrombocytopenia (USMEC Category 3 for initiation of DMPA; USMEC Category 2 for continuation of DMPA)
- Rheumatoid arthritis on long-term corticosteroid therapy with a history of, or with risk factors for, nontraumatic fractures
- Unexplained vaginal bleeding before evaluation
- Past breast cancer with no evidence of current disease for 5 years
- Diabetes with nephropathy, retinopathy, or neuropathy
- Diabetes of >20 years duration
- Severe cirrhosis of the liver
- Liver tumor (hepatocellular adenoma or malignant hepatoma)

Absolute (USMEC Category 4 – A Condition That Represents an Unacceptable Health Risk if the Contraceptive Method Is Used)

- Current breast cancer

Counseling Tips

- No rubbing of the injection site after administration.
- Expect to have changes in the menstrual cycle including irregular bleeding and amenorrhea. These bleeding patterns are not worrisome or harmful.

- The longer DMPA is used, the more common amenorrhea is.
- If the pattern of bleeding is excessive or worrisome, the user should contact the health care provider.
- Minor side effects of breast tenderness, nausea, mood changes, or headaches typically decrease after several months of use.
- When discontinuing DMPA, the median duration of return to ovulation is 10 months following the last injection.
- Limiting caloric intake and increasing exercise is important, especially for users complaining of weight gain. With continued weight gain after attempts to limit calorie intake and increase exercise have failed, switching to another contraceptive method may be advised.

Instructions for Use

- 150 mg DMPA is administered intramuscularly into the deltoid or gluteal muscles once every 3 months (13 weeks).
- 104 mg Depo-subQ is administered by subcutaneous injection into the anterior thigh or abdomen once every 3 months (13 weeks). Depo-subQ is neither formulated for intramuscular injection nor labeled for self-administration.

Screening Tests

There are no examinations or tests that are needed before starting DMPA in healthy women.

A baseline weight measurement may be useful for monitoring any change in weight on the method. According the United States Selected Practice Recommendations on Contraceptive Use, released in 2013 by the CDC, blood pressure measurement is not necessary due to the low prevalence of undiagnosed severe hypertension in the population [1].

Timing of Initiation

- Within 7 days of the onset of menses
  - No back-up contraception is needed.
- Any time in the menstrual cycle as long as it is reasonably certain that the woman is not pregnant
  - Back-up contraception or abstinence should be used for 7 days.

- The same day emergency contraceptive pills are given
  - Back-up contraception or abstinence should be used for 7 days and a repeat pregnancy test should be performed in 2–4 weeks.
- Postabortion: Initiate immediately or within the first 7 days
  - If not given immediately, then back-up contraception should be used for 7 days.
- Postpartum nonbreastfeeding: After delivery, DMPA can be started at any time, including immediately postpartum.
  - If ≥21 days postpartum without return of menses, back-up contraception or abstinence should be used for 7 days.
- Postpartum breastfeeding: After delivery, DMPA can be started at any time, including immediately postpartum.
  - If the woman is <6 months postpartum, amenorrheic, and exclusively breastfeeding, no back-up contraception is needed.
  - If the woman is more than 21 days postpartum and not using DMPA with lactational amenorrhea, then back-up contraception should be used for 7 days after injection [1].
- Switching from another contraceptive method
  - Initiate immediately as long as it is reasonably certain that the woman is not pregnant.
  - If more than 7 days since the onset of menses, back-up contraception or abstinence should be used for 7 days.

Repeat Injections

Repeat injections of DMPA should be scheduled every 3 months (13 weeks). After a 150-mg injection, ovulation does not occur for at least 14 weeks. A 2-week grace period is appropriate for women receiving injections every 3 months (up to 15 weeks) [1]. In women more than 2 weeks late for an injection, a urine pregnancy test should be performed before administering further DMPA and back-up contraception for 7 days is advised.

Managing Side Effects

Bleeding

Bleeding irregularities occur in almost all women using DMPA and are the most common reason for discontinuation of DMPA (25% of users in the first year) [61].

Episodes of unpredictable bleeding and spotting lasting a week or longer are common. "Breakthrough" bleeding is experienced by 90% of users during the first 3 months of DMPA use [62] and has been reported to occur on 20–30% of days during the first 6 months of DMPA use [63]. The frequency and duration of irregular bleeding decreases with increasing duration of DMPA use, with 46% of women achieving amenorrhea after 1 year of use [14, 64].

The high rate of irregular bleeding often leads to premature discontinuation of DMPA, potentially increasing risk of unintended pregnancies. Enhanced counseling among DMPA users detailing expected bleeding patterns and reassurance that these irregularities generally are not harmful and are not associated with decreased contraceptive efficacy has been shown to reduce DMPA discontinuation in clinical trials [65, 66].

While irregular bleeding can be a side effect of DMPA, other causes of bleeding may need to be investigated depending on the clinical situation. For example, pregnancy, cervicitis or cervical dysplasia, STIs, and uterine conditions such as a fibroid, polyp, endometrial hyperplasia, or cancer are all possible causes of bleeding [1].

The etiology of irregular bleeding in DMPA users is not clearly understood. One proposed mechanism relates to endometrial tissue regulation. Angiogenesis is key to this process, and one of its stimulants is estradiol. Fluctuating estrogen levels associated with the use of DMPA may lead to enough transcription of angiogenesis growth factors to stimulate the development of dilated venules under the endometrial surface. Concurrently, the nonvascular elements of the endometrium regress with continuous progesterone exposure, resulting in an endometrium with increased and disordered microvessels, decreased stromal and glandular support, and reduced epithelial integrity. This results in increased superficial endometrial vascular fragility, instability of the endometrium, and ultimately breakthrough bleeding [67].

Because the frequency and duration of irregular bleeding typically decreases with continued DMPA use, first line intervention for bleeding irregularities among DMPA users is reassurance and counseling. For women who desire an intervention, treatment options for DMPA-associated irregular bleeding are described below.

Use of a nonsteroidal anti-inflammatory (NSAID) medication for 5–7 days has been shown to decrease DMPA-associated bleeding and is endorsed by the 2016 US Selected Practice Recommendations for Contraceptive Use [31].

Although data supporting the use of the NSAID mefenamic acid for the treatment of DMPA-associated irregular bleeding is limited, a small double-blind placebo-controlled study concluded that mefenamic acid 500 mg orally twice daily for 5 days was more effective than placebo, in controlling bleeding during the first week of DMPA use (69.6% vs 40.0%, $p < 0.05$). However, at the 4-week follow-up, the mean bleeding-free interval was not statistically different between the mefenamic acid group and the placebo group (16.1 and 12.4 days, $p > 0.05$) [68].

A double-blind placebo-controlled Thai study examined the use of the antifibrinolytic tranexamic acid in 100 DMPA users with irregular bleeding and found that tranexamic acid was more effective than placebo in the short-term treatment of irregular bleeding associated with DMPA use. The treatment group received tranexamic acid 250 mg orally four times a

day for 5 days and the control group received placebo in the same manner. When compared to the placebo group, the tranexamic acid group had a significantly higher percentage of women in whom irregular bleeding stopped during the first week of treatment (88% vs 8.2%, $p < 0.001$). During the 4-week follow-up period, a bleeding-free interval of >20 days was found in 68% of subjects treated with tranexamic acid and 0% treated with placebo ($p < 0.001$). The mean number of bleeding/spotting days was also significantly different between the groups (5.7 +/− 2.5 vs 17.5 +/− 7.2 days, $p < 0.05$) [69].

Estrogen supplementation is thought to promote endometrial tissue repair and coagulation. The efficacy of supplemental estrogen for the prevention or treatment of DMPA-associated unscheduled bleeding is unclear, as trials have reported discordant findings and some were flawed by high discontinuation rates among study participants.

Options for supplemental estrogen include the following: Conjugated estrogen 1.25 mg or micronized estradiol 2 mg orally for 7–10 days; transdermal estrogen patch releasing 0.1 mg estradiol/24 hours; or 10–20 days of a monophasic low-dose combined oral contraceptive pill (<50 mcg of estrogen).

The addition of estrogen does not affect the contraceptive efficacy of DMPA, but it does put the patient at risk for estrogen-related side effects [70].

One randomized placebo-controlled trial demonstrated that low doses of the antiprogestin mifepristone decreased the number of days of unscheduled bleeding in women initiating DMPA. The study evaluated 20 new users of DMPA and found that 15% of women taking mifepristone 50 mg orally every 2 weeks experienced unscheduled bleeding during the first 3 months of use, compared with 36% of women taking placebo. The effect of mifepristone may be due to a functional inhibition of progesterone, which results in an upregulation of endometrial estrogen receptors that induce factors responsible for endometrial proliferation and bleeding cessation [71]. If mifepristone is used for this purpose, a back-up method of contraception should be used for 14 days [72]. A low-dose formulation of mifepristone is not available in the United States.

Anecdotally, some clinicians opt to shorten the intervals between DMPA injections to reduce unscheduled bleeding, however, there is no published evidence to support this practice [72].

Tips on Cost and Insurance Issues

The Affordable Care Act currently requires all insurance plans to cover contraceptive counseling and education, and provision of FDA-approved contraceptive methods, including DMPA. Administration is currently only available in health care clinics and similar settings. Because IM DMPA is available as a generic formulation, for many users it may be substantially less expensive than the subcutaneous formulation.

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Chapter 7
Implantable Contraception

Valerie French

Introduction

Contraceptive implants are progestin-based, highly effective, and rapidly reversible methods of contraception that require little of the user and have few side effects.

Over the past 35 years, they have been approved in more than 60 countries and used by millions of women worldwide [1]. Their high efficacy along with ease of use makes them a good contraceptive option for women of all ages who require progestin-only methods, desire highly effective contraception, as well who desire long-term protection. In most countries, two different contraceptive implants are available: the single rod etonogestrel implant and the two-rod levonorgestrel system. The pharmacological profile and physical effects of all the implantable contraceptives are similar. While the etonogestrel implant is the only form of implantable contraception available in the United States (and the focus of this chapter), clinicians may encounter other systems in use worldwide.

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History of Implantable Contraception

Norplant, a six-capsule implantable system containing 216 mg of levonorgestrel, was developed by the Population Council and first approved in 1983 in Finland, where it was manufactured. The United States' FDA approved the device in 1990, but the distributor withdrew it from the market in 2002. Over one million US women had chosen Norplant as their contraceptive. Norplant proved highly effective; over a 7-year duration of use, approximately 1% of users became pregnant [2]. Despite low rates of pregnancy and few serious side effects, limited supplies of the silastic components and unwarranted negative media coverage led to Norplant's withdrawal from distribution in 2002, leaving no implant alternative for American women [3]. Production of Norplant was discontinued worldwide in 2008.

The 15-year experience with Norplant instigated further development and improvements in implant design. A two-rod LNG system (Jadelle) was also developed by the Population Council and manufactured in Finland. It was approved in the United States in 1998, but never marketed. Jadelle is effective for 5 years and was first registered for this length of use in the year 2000. Sino-implant (II) is a two-rod implant system designed to imitate the performance of Jadelle. It is manufactured in China and is substantially less expensive to manufacture than Jadelle (US$8 compared with US$23) [4]. This levonorgestrel implant has the potential to improve access to contraceptive implants in resource-poor settings.

In 2006, the US Food and Drug Administration approved Implanon, a single-rod etonogestrel implant. Implanon's single rod provided great improvements over the previously available six-capsule Norplant system in time and ease of insertion [5, 6]. The etonogestrel implant inserter is preloaded and disposable. Since only one rod is implanted, there is no chance of moving previously placed capsules out of position with insertion of additional ones. It is not necessary, as it was with Norplant, to create channels under the skin with a local anesthetic, which made implants difficult to palpate right after insertion. In addition, ethylene vinyl acetate, the plastic from which Implanon is made, is less likely than Norplant's silastic to form a fibrous sheath that can prolong removals [7]. These differences simplify the insertion and removal technique for the etonogestrel implant. For patients, this simplicity means little discomfort at insertion or removal, an unobtrusive implant, and almost no scarring. For clinicians, it means simpler insertion and removal procedures of a predictably short duration. The etonogestrel implant has subsequently been modified and marketed as Nexplanon. In December 2012, Merck stopped supplying Implanon to its distributers, whose supply was exhausted in early 2013. Implanon is no longer available for purchase in the United States. Implanon and Nexplanon are bioequivalent, but Nexplanon is radio-opaque and is pre-loaded into a simpler inserter that helps ensure subdermal placement.

Candidates for Implantable Contraception

Contraceptive implants are a good choice for women of reproductive age who are sexually active and desire highly effective contraception.

Most women are candidates for implantable contraception; there are few medical disorders where the risk of the method exceeds the benefit (e.g., current breast cancer). For clinicians in the United States, the Centers for Disease Control and Prevention (CDC) has listed these conditions in the table, "United States Medical Eligibility Criteria (USMEC) for Contraceptive Use" [8]. Large epidemiologic studies have not identified an increased risk of stroke, myocardial infarction, or venous thromboembolism in users of progestin-only oral contraceptives [9–11], and none of these events occurred in any of the trials on which approval of the implants was based [11, 12]. Subsequently published data support this conclusion [13].

For this reason, the World Health Organization (WHO) and the CDC have indicated that progestin-only contraceptives represent a reasonable contraceptive choice for women with risk factors for, or a past history of, venous thromboembolic disease [8].

This recommendation differs from Nexplanon package labeling, which lists current or past thrombosis as a contraindication to use. Etonogestrel is the biologically active metabolite of the synthetic progestin desogestrel. Controversy remains as to whether desogestrel or its derivatives may be associated with an increased risk of venous thromboembolism compared with other progestins. Evidence of this increased risk comes from studies of oral contraceptives where desogestrel is administered in combination with ethinyl estradiol, rather than alone as in the implant [14]. A randomized controlled trial of maternal hemostasis during the 6-week postpartum period found no increase in coagulation factors for women using the etonogestrel implant when compared to women with no hormonal contraception, supporting the safety of the method in women at increased risk for thrombotic events [15].

Women with Chronic Medical Conditions

Implant contraceptives can be a good choice for women with chronic illnesses because there are no clinically significant metabolic changes associated with the sustained, low doses of progestin delivered by the implant.

Studies of liver function, blood coagulation, immunoglobulin levels, serum cortisol levels, and blood chemistries have failed to detect changes outside of normal ranges and the etonogestrel implant has not been found to have important clinical effects on the lipoprotein profile, carbohydrate metabolism, thyroid and adrenal function, liver function, or the clotting mechanism [16–19]. A literature review concluded that the etonogestrel implant does not appear to have clinically significant effects on lipid metabolism or liver function, although there may be small changes in laboratory values [20]. These findings suggest that implant contraceptives are safe for woman at risk for metabolic, cardiovascular, or thromboembolic disorders.

For women with diabetes whose disease is well controlled by insulin or diet, implant contraceptives are a safe option. Although progestins can affect carbohydrate metabolism, most effects are seen with high doses of androgenic progestins, not the low doses found in implants or with the less androgenic etonogestrel. Few studies have evaluated carbohydrate metabolism in women with the etonogestrel implant, although one prospective study found that there was no difference in fasting glucose, oral glucose tolerance test, and hemoglobin A1C levels at 12 months in women who use the etonogestrel implant [21].

Lactating Women

As progestin-only methods, the contraceptive implants are a safe option for breastfeeding women because they do not interfere with breast milk production. Studies show no effects on breast milk quality or quantity, and infants of mothers with implants grow normally [22, 23]. Implants also seem to be a good choice for immediate post-partum administration. A small study comparing immediate postpartum insertion of the etonogestrel implant to depot medroxyprogesterone acetate at 6 weeks showed no impact on continuation of exclusive breastfeeding at 12 weeks and normal infant weight gain [24]. The etonogestrel implant does not affect breastfeeding outcomes when placed in the immediate post-partum period (within 1–3 days of delivery) compared with delayed insertion (4–8 weeks) [25, 26]. Immediate placement has also been found to be cost-effective when compared with delayed insertion [27].

Adolescents

Adolescents are candidates for contraceptive implants. This method that does not require repeated adherence and offers a discrete method of highly effective contraception. Adolescents most frequently use methods with high failure rates, including condoms, withdrawal, and oral contraceptive pills [28]. Long-acting reversible contraception, including implants and intrauterine devices, has a high uptake among adolescents, with younger adolescents choosing the implant more commonly [29].

The etonogestrel implant is well accepted by postpartum adolescents as well [30]. Women under the age of 18 years have no medical contraindication to implantable contraception based on age alone and the American College of Obstetricians and Gynecologists recommends including implants when discussing contraception with adolescents [8, 31]. Recent studies indicate that use of implantable contraception has been increasing, particularly among adolescents [32].

Pharmacology

The Nexplanon implant is 40 mm × 2.0 mm and consists of one nonbiodegradable rod of 40% ethylene vinyl acetate and 60% etonogestrel (the 3-keto derivative of desogestrel), covered with a rate-controlling ethylene vinyl acetate membrane 0.06 mm thick. The rod contains 68 mg of etonogestrel that is slowly released over at least 3 years: initially at 60–70 mcg/day, decreasing to 35–45 mcg/day at the end of the first year, to 30–40 mcg/day at the end of the second year, and then to 25–30 mcg/day at the end of the third year (Fig. 7.1) [33]. The high initial rate of absorption is probably due to a significant amount of etonogestrel released from the uncovered ends of the implant. Peak serum concentrations (266 pg/mL) of etonogestrel are achieved within 1 day after insertion, suppressing ovulation, which requires only 90 or more pg/mL [34, 35].

Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and 66% bound to albumin in blood. Like other contraceptive steroids, serum levels of etonogestrel are reduced in women taking liver enzyme-inducing drugs such as rifampicin, griseofulvin, phenytoin, and carbamazepine, but are

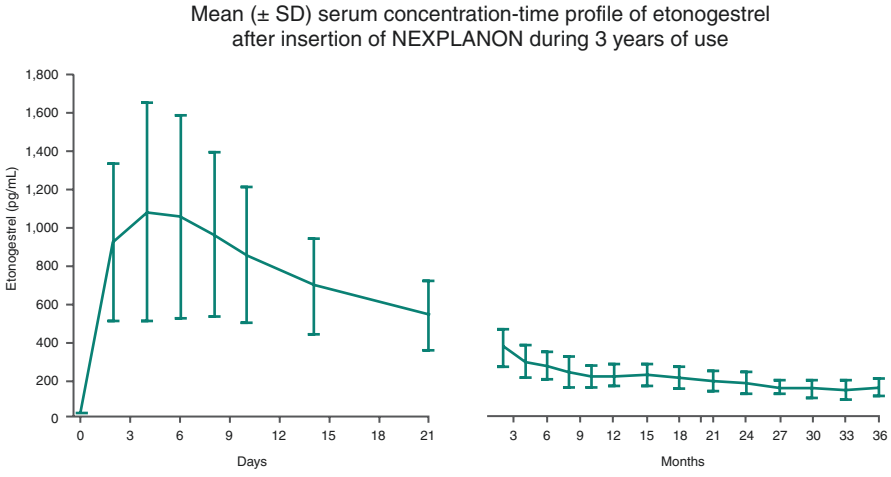

Fig. 7.1 Mean (±SD) serum concentration-time profile of etonogestrel after insertion of Nexplanon during 3 years of use

not affected by antibiotics. Steady release of etonogestrel into the circulation avoids first-pass effects on the liver. Bioavailability of etonogestrel remains nearly 100% throughout 2 years of use. The elimination half-life of etonogestrel is 25 hours. After implant removal, serum etonogestrel concentrations become undetectable within 1 week. Return of ovulation occurs in 94% of women within 3–6 weeks after method discontinuation [34, 35]. Unlike Implanon or the levonorgestrel implants, the Nexplanon rod is radio-opaque, so it can be detected by X-ray and does not require magnetic resonance imaging (MRI) for locating an non-palpable implant.

Mechanism of Action

Progestin diffuses from the implant into the surrounding tissues where it is absorbed by the circulatory system and distributed systemically, providing an initial level in the circulation that is lower than with oral or injected steroids. The release rate of the contraceptive implants is determined by total surface area and the density of the plastic (Silastic or EVA) in which the progestin is contained. Progestin-containing implants have two primary mechanisms of action: inhibition of ovulation and restriction of sperm penetration through cervical mucus [36]. Antiestrogenic actions of the progestins affect the cervical mucus, making it viscous, scanty, and impenetrable by sperm, thus inhibiting fertilization [37]. At high doses, progestins also inhibit gonadotropin secretion, thereby inhibiting follicular maturation and ovulation [38]. The etonogestrel implant inhibits ovulation for 3 years, accounting for almost all of its contraceptive effect [1]. Although progestins suppress endometrial activity making the endometrium unreceptive to implantation, this is not a contraceptively important effect since the major mechanisms of action prevent fertilization [34]. No signs of embryonic development have been found among implant users, indicating that progestin implants have no abortifacient properties.

Efficacy

General Population

The etonogestrel implant is among the most effective contraceptives available (Table 7.1), as good or better than sterilization procedures [38].

An analysis of 11 clinical trials in which 942 women enrolled for 2–4 years showed that the etonogestrel implant was well tolerated and effective: no pregnancies occurred while women were using this method of contraception [12]. Six pregnancies

Table 7.1 Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year in the United States

	Percentage of women experiencing an unintended pregnancy within the first year of use		
	Typical use[b]	Perfect use[c]	Percentage of women continuing use at 1 year[a]
Method			
No method[d]	85	85	–
Spermicides[e]	28	18	42
Fertility awareness-based methods[f]	24	0.4–5	47
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Male condom[g]	21	5	41
Female condom[g]	18	2	43
Diaphragm[h]	12	6	57
Combined pill and progestin-only pill	9	0.3	67
Combined patch	9	0.3	67
Combined ring	9	0.3	67
DMPA	6	0.2	56
Copper IUD	0.8	0.6	78
Levonorgestrel IUD	0.2	0.2	80
Etonogestrel implant	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.1	100

Adapted from Trussell [5]

[a]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year

[b]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

[c]Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

[d]The percentages becoming pregnant are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether

[e]Foams, creams, gels, vaginal suppositories, and vaginal film

[f]Includes the Ovulation, TwoDay, Standard Days, and Symptothermal methods

[g]Without spermicides

[h]With spermicidal cream or jelly

Table 7.2 Extended use data and number of events by year and cohort

	LNG implant	ETG implant	Copper IUD
Number of pregnancies in the first three years[a]	3	3	14
Extended 4-year data			
Number of women starting	522	390	416
Number of women completing	470	311	373
Woman-months of observation	6254	4606	4995
Number of pregnancies	0	0	1[b]
Extended 5-year data			
Number of women starting	470	311	373
Number of women completing	330	204	256
Woman-months of observation	4629	2454	3521
Number of pregnancies	0	0	2
Year 1–5 cumulative data			
Total woman-months of observation	30,325	22,044	24,134
Total number of pregnancies for 5 years of observation	3	3	17
Cumulative pregnancy rates[b] (Kaplan Meier Rates)	0.8 (0.2–2.3)	0.6 (0.2–1.8)	4.1 (2.5–6.5)

Table from: Ali et al. [39]
LNG levonorgestrel, *ETG* etonogestrel
[a]Number of pregnancies reported previously in Bahamondes et al. (2015) in the first 3 years [79]
[b]One additional pregnancy that occurred around 36 months was reported above. The Kaplan–Meier (K–M) method was used to estimate the overall cumulative pregnancy rates

have been reported during the first 14 days after implant removal. The manufacturer cites a Pearl Index of 0.38 pregnancies per 100 women-years of use, effectiveness similar to that of other long-acting methods of contraception. Post-marketing data indicate that the etonogestrel implant's efficacy at pregnancy prevention continues as long as 5 years (Table 7.2) [39, 40]. In the rare event of failure, pregnancy may be intrauterine or extrauterine [41]. Because compliance does not require frequent resupply or instruction in use as necessary with oral contraception, the actual or typical use effectiveness is very close to the theoretical (lowest expected) effectiveness.

Overweight and Obese Women

The etonogestrel implant is not contraindicated in obese women [8].

Although the effectiveness of the etonogestrel implant has not been adequately studied in women more than 130% of their ideal body weight (body mass index [BMI] greater than 30 kg/m^2), available data show no decrease in contraceptive

efficacy even though lower plasma etonogestrel concentration is seen in obese women [42, 43]. Etonogestrel concentrations do not decline below contraceptive levels as body weight increases, nor is there an increased risk of difficult insertions or removals with increasing BMI [due to superficial insertion] [44].

Drug Interactions Impacting Efficacy

Contraceptive efficacy may be decreased in women taking medications that affect the metabolism of etonogestrel [45]. Two case reports describe contraceptive failure in women on carbamazepine for epilepsy; both women had an etonogestrel implant in place for over 18 months [46, 47].

Contraceptive failures have been described for women living with human immunodeficiency virus (HIV) while using the etonogestrel implant and taking efavirenz-based antiretroviral therapy [48]. All implants appeared to be correctly positioned and there was no obvious reason for the contraceptive failures other than a possible decrease of etonogestrel efficacy related to administration of efavirenz, a hepatic enzyme-inducing antiretroviral medication. Pharmacokinetic studies of the etonogestrel implant in women on antiretroviral medications showed substantial decreases in the bioavailability of etonogestrel in women on efavirenz-based and nevirapine-based regimens, whereas women on a lopivanir-based regimen had increased bioavailability of etonogestrel. [49, 50]

Emerging evidence also suggests that efavirenz-based antiretroviral regimens affect levonorgestrel levels more profoundly, resulting in higher contraceptive failure rates [51, 52]. In one retrospective study of HIV-positive women with the levonorgestrel implant, one of the 221 women on nevirapine or lopinavir/ritonavir-based regimens became pregnant, whereas 15 of the 121 women on efavirenz became pregnant [52]. Neither nevirapine-based regimens nor tenofovir disoproxil fumarate-emtricitabine regimens have been shown to alter levonorgestrel levels [51, 53].

Although it is not currently possible to assess the magnitude of the risk of contraceptive failure in this setting, prospective users taking antiretrovirals should be informed that efavirenz use accelerates etonogestrel and levonorgestrel metabolism and greatly increases implant failure rates. From the available evidence on the etonogestrel implant in women taking efavirenz, it appears that the contraceptive failures occur later within the 3 years that the device is efficacious, possibly due to a more rapid depletion of etonogestrel levels.

The accelerated metabolism of progestin does not preclude use of implants, which remains highly effective for most women on antiretroviral and antiepileptic

Some experts have suggested replacing implants early or placing more than one implant for women on efavirenz due to the decreased levonorgestrel or etonogestrel levels, but these practices have not been studied.

drugs. Furthermore, HIV-positive women are typically advised to use condoms to protect against transmission of HIV and other sexually transmitted infections; thus, they typically have back-up contraceptive protection.

Counseling

Irregular Bleeding

Unscheduled bleeding is a common side effect, which may or may not decrease with continued use. Because implants allow for follicular development but not ovulation, endogenous estrogen production is nearly normal, and unlike the combined estrogen–progestin contraceptives, progestin is not regularly withdrawn to allow endometrial sloughing. Consequently, the endometrium sheds at unpredictable intervals and menstrual bleeding patterns can be highly variable among users of implant contraception. Changes include alterations in the interval between bleeding, the duration, and volume of menstrual flow, and spotting.

> In the analysis of 11 clinical trials, unscheduled bleeding was the primary reason for discontinuation, with a rate of 14.8 percent in the United States and Europe, but only 3.7 percent in Southeast Asia, Chile, and Russia [12]. United States users were more likely to discontinue because of prolonged or heavy bleeding than women from other countries (7.0 versus 4.3 percent). The mean number of bleeding and spotting days per 90-day reference period was 7.3 and 10.4 days, respectively. One-third of 90-day reference periods had fewer than three bleeding/spotting episodes; one-fifth had no bleeding/spotting (amenorrhea); 17 percent had a bleeding episode that lasted more than 14 days, and 6 percent had more than five bleeding/spotting episodes. The number of unscheduled bleeding days was highest in the first three months of use, decreased during the first year of use, and then plateaued for the second and third years of use. However, this decrease may have resulted from patients discontinuing as a result of a bleeding irregularity, leaving for analysis those less likely to experience bleeding. Although amenorrhea occurs in approximately 20% of women in the first year of use, the rates of amenorrhea actually decline with duration of use to 13% by year 3 [54].
>
> Women who experienced more days of bleeding were more likely to discontinue, especially if the bleeding was prolonged. For example, the mean number of bleeding/spotting days in women who discontinued and who continued implant use during a 90-day reference period was 45.2 and 16.5 days, respectively. Frequent or prolonged bleeding/spotting was reported in about 90 percent of women who discontinued the implant but in only 22 percent of those who continued its use [55].

Management of Irregular Bleeding

Treatment of unscheduled bleeding is not necessary, but since bleeding disturbances are the principal cause of discontinuation, several approaches to their treatment have been used. For women who have no contraindications to estrogen, prolonged bleeding may be treated with a short course of oral estrogen: conjugated estrogens,

1.25 mg, or estradiol, 2 mg, administered daily for 7 days [56]. An alternative approach is to administer an estrogen–progestin oral contraceptive for 1–3 months. One randomized controlled trial found that a 7-day course of tamoxifen 10 mg twice daily decreased the number of bleeding/spotting days that women experienced during breakthrough bleeding with the etonogestrel implant [57]. Another randomized controlled trial found that etonogestrel implant users who were treated with 7 days of daily ulipristal acetate 15 mg had a reduced number of bleedings days and higher satisfaction with their bleeding profile when compared to those treated with placebo [58]. Short courses of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for 5–7 days have also been recommended to manage irregular bleeding [59]. Clinicians have many tools to manage women who experience bleeding disturbances with the etonogestrel implant.

Other Side Effects

The most common adverse events besides unscheduled bleeding that were deemed possibly, probably, or definitely related to the etonogestrel implant included headache (16%), weight gain (12%), acne (12%), breast tenderness (10%), emotional lability (6%) and abdominal pain (5%) [12].

The etonogestrel implant does not induce bone loss. In contrast, depot medroxyprogesterone acetate (DMPA), another progestin-only contraceptive that reduces estrogen levels, can decrease bone mineral density.

A large epidemiologic study using registry data from Denmark did not find an increased risk of arterial events among 24,954 implant users compared with over 9 million nonusers of hormonal contraception [13]. For thrombotic stroke, there were three events among users, incidence 12/100,000 person years, RR 0.88, 95% CI 0.28–2.72; for myocardial infarction, there were three events among users, incidence 12/100,000 person years, RR 2.14, 95% CI 0.69–6.65.

Sexually Transmitted Infections

Sexually active women are exposed to the risk of pregnancy as well as to the risk of sexually transmitted infections (STIs), such as HIV, hepatitis B, human papillomavirus, *Chlamydia trachomatis*, syphilis, and gonorrhea whose sequelae may be life-threatening. Implantable contraceptives neither increase the risk of nor offer protection against STIs [60]. Women counseled about contraception should also be informed about the risks of STIs. They should be advised that use of condoms concomitantly with an effective method of pregnancy prevention is the best means of protection against unintended pregnancy and STIs. It seems likely that the etonogestrel implant, like oral contraceptive pills and DMPA, reduces the risk of pelvic upper tract infection (PID), probably because of progestin effects on cervical mucus.

Some evidence suggests that DMPA use increases the risk of human immunodeficiency virus (HIV) acquisition [61]. There is no evidence that other contraceptive progestins at lower doses, such as the etonogestrel implant, have similar effects.

Initiation

For healthy women, no physical examination or laboratory tests are indicated before insertion of an etonogestrel implant [59].

Although some medical conditions represent contraindications to hormone use [8], the low prevalence of these conditions in women of asymptomatic reproductive age does not warrant screening for these conditions by physical examination or laboratory testing for the safe initiation of implants [59].

The possibility of early pregnancy can generally be assessed by review of the woman's menstrual, sexual, and contraceptive history. The absence of pregnancy can be reasonably inferred if she meets any of the criteria in (Box 1). An appropriately timed pregnancy test (at least 2 weeks after the last episode of sex) can be obtained if the absence of pregnancy is uncertain.

There is no evidence that the etonogestrel implant or other hormonal contraceptives have caused abnormal fetal development. Most of the few pregnancies reported among etonogestrel implant users were present before insertion. The implant can be inserted at any time as long as the clinician is reasonably certain that the patient is not pregnant. Women who are postabortion (either medical or surgical) or postpartum (even if breastfeeding) can have the implant inserted immediately after termination of pregnancy or delivery [8].

Back-Up Contraception

Abstinence or back-up contraception is suggested for the first 7 days after insertion if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period [59], although data to support this need are lacking [62]. This conservative approach is recommended because changes in cervical mucus occur rapidly and are probably complete within 36 hours of insertion. Options for back-up contraception include use of condoms or continued use of the woman's previous method of contraception. For women who are postpartum, not exclusively breastfeeding, and have not resumed menses, back-up contraception is suggested for those who are more than 3 weeks postpartum. For women who are postpartum,

exclusively breastfeeding, and have not resumed menses, back-up contraception is suggested for those who are more than 6 months postpartum. For women who are post-abortion, back-up contraception is suggested if the implant is not placed on the day of the abortion.

If the woman has been using an intrauterine device (IUD) and is switching to the implant, she may have residual sperm in her reproductive tract, which could result in fertilization and implantation if the IUD is removed. Options include the following:

- Advise the woman to retain the IUD for at least 7 days after the implant is inserted and then return for IUD removal.
- Advise the woman to abstain from sexual intercourse or use barrier contraception for 7 days before removing the IUD and switching to the implant. Back-up contraception is suggested if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period.
- Advise the woman to use emergency contraception at the time of IUD removal and use back-up contraception if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period.

Insertion

Insertion of Nexplanon is a brief office procedure performed under local anesthesia. A clinician who has been trained in the technique can do it in less than 1 minute [63]. The US Food and Drug Administration (FDA) and Nexplanon's maker, Merck, agreed that Implanon and Nexplanon would be distributed only to clinicians who have received 3 hours of training in patient selection, counseling, insertion, and removal. Questions regarding training can be answered at 1-877-467-5266. Merck is required to coordinate and provide instructors and materials for training, as well as to monitor clinician reporting of adverse events. This voluntary reporting system has not revealed any unexpected problems with insertion or removal of the etonogestrel implant [64]. In 2018, Merck updated the recommended insertion location to avoid the blood vessels and nerves that lie in the biceps groove.

Required Equipment for Etonogestrel Implant Insertion

- A 25-gauge needle (1.5 inches in length) attached to a 2–5 mL syringe
- 1% chloroprocaine or lidocaine without epinephrine
- Antiseptic solution (e.g., povidone iodine, chlorhexidine gluconate, isopropyl alcohol)
- An adhesive strip for closure of the puncture site
- Elastic pressure bandage (e.g., "Kerlex")

- Surgical gloves (need not be sterile)
- Sterile drape
- Sterile, preloaded Nexplanon applicator

Positioning the Patient

The patient is placed in a supine position with the full length of her arm exposed. The manufacturer suggests positioning the upper inner arm by bending the elbow to 90° and rotating the arm out. Some providers find the procedure is easier when the arm is extended, allowing full exposure of the crease between the biceps and triceps muscles. Adequate support under the arm should be provided to ensure comfort with, e.g., a pillow. In 2018, Merck updated the recommended insertion location to avoid the blood vessels and nerves that lie in the biceps groove. The insertion site overlies the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the sulcus between the biceps and triceps muscles (Fig. 7.2). The optimum site depends upon an individual woman's anatomy, such as the length of the upper arm (avoid placing the end of the implant too near the axilla) and the area where the crease between the biceps and triceps muscles is clearest.

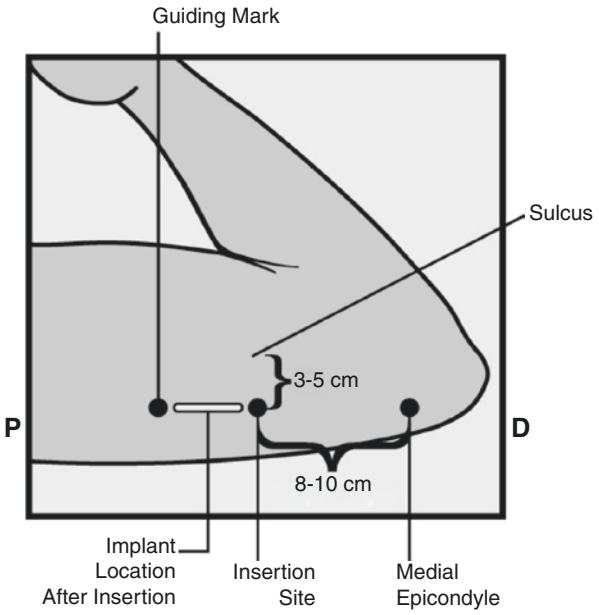

Fig. 7.2 The insertion site is overlying the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the sulcus (groove) between the biceps and triceps muscles

To minimize the risk of infection, strict aseptic technique should be maintained throughout the procedure, e.g., do not touch the trocar containing the implant. A sterile drape is placed under the arm, and the insertion site on the arm is cleaned with an antiseptic such as povidone-iodine. Some clinicians mark the skin to help guide insertion. One mark is made where the rod will be inserted, and a second mark is made a few centimeters proximal to the first mark to serve as a direction guide during insertion. However, insertion directly through the marked skin should be avoided as it can result in "tattooing." Use of skin marks is at the clinician's discretion.

Anesthesia

Local anesthesia for the incision is obtained by raising a wheal of 1% chloroprocaine or lidocaine using a 1½ inch 25-gauge needle and injecting 1–3 ml under the skin along the track of the implant insertion needle. A burning sensation is common during injection of the local anesthetic. This effect can be eliminated for most patients by adding 1 meq of sodium bicarbonate to each 10 mL of anesthetic (however, this buffering shortens shelf life to 24 hours) [65]. Local anesthesia should be allowed a few minutes to take effect and the insertion site should be tested prior to beginning the procedure to ensure that the patient is comfortable.

Insert Implant

The operator should view the insertion site from the side, not from above the device. Most women feel no more than a pressure sensation during the insertion procedure. The sharp, beveled trocar easily penetrates the skin, making a separate scalpel incision unnecessary. Grasp the applicator above the needle cap on its textured surface between thumb and forefinger. Remove the clear plastic needle cover. Place the needle against the insertion site holding the applicator at an angle 30° to the skin (Fig. 7.3). While applying counter traction to the skin around the insertion site, puncture the skin with the needle tip. Lower the applicator so that it is parallel to the skin and advance the needle in the subdermal connective tissue while lifting the skin with the tip of the needle. Advance the needle to its full length. If the needle is not fully advanced under the skin, the implant will not be correctly inserted. Unlock the slider with downward finger pressure on the lever, then move the slider fully backward (distally) and withdraw the needle.

Verify Placement

Immediately after insertion, palpate the skin to verify correct placement of the rod; both ends should be palpable. Ask the patient to feel her implant, then place an adhesive closure on the insertion puncture and wrap the site with a pressure bandage

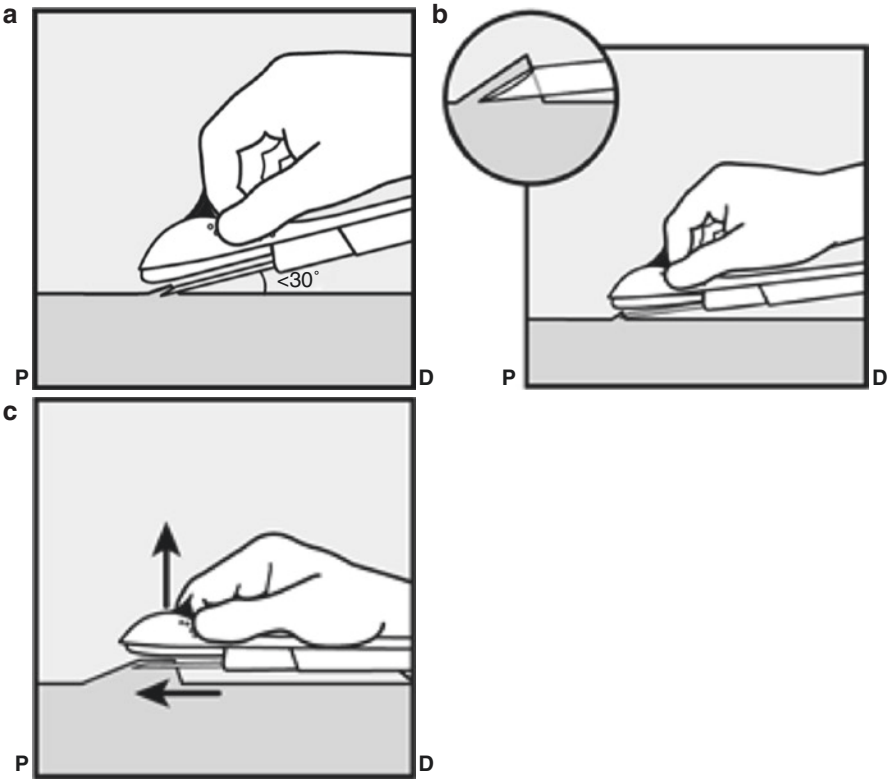

Fig. 7.3 (**a**–**c**) Grasp the applicator above the needle cap on its textured surface between the thumb and forefinger. Remove the clear plastic needle cover. Place the needle against the insertion site holding the applicator at a 30° angle to the skin

to minimize bruising. If you cannot feel the implant, check the applicator to make sure the implant is no longer in the applicator. The applicator obturator is purple, while the implant is white. If there is doubt about the presence of the implant, use sonography or an X-ray to determine its presence. Magnetic resonance imaging (MRI) is not required.

Post-Insertion Care and Follow-Up

Complete the Patient Chart Label for the patient's medical record and the User Card, which must be given to the patient. The woman may remove the pressure bandage in 24 hours and the small bandage in 3 days. Most women do not experience pain after insertion, but if it occurs, aspirin, acetaminophen, or nonsteroidal anti-inflammatory agents usually provide relief. The patient may be discharged

immediately after the procedure. A routine follow-up visit is not necessary [59]. She should call the provider if she develops pain, discharge, or swelling at the insertion site, fever, or other concerns. She should also contact her provider if she has a change in her health status that could affect safe and effective use of this method, or when she wants to switch contraception methods, remove the implant to attempt pregnancy, or replace the implant when efficacy wanes.

Complications of Insertion

Complications are rare, reported in 0.3–1% of insertions and 0.2–5.9% of removals [64, 66, 67]. Potential complications include infection, hematoma formation, local irritation or rash, expulsion, and allergic reactions. The implant may migrate a short distance (less than 2 cm) over time [68]. The incidence of complications is minimized by clinician training and experience, and the use of strict aseptic technique. Incorrect placement can result in nerve injury or neuropathy [69]. In very rare cases, improper placement can result in implant migration to the vasculature, chest wall, or distant body sites [70]. When placed by a trained clinician, complications of etonogestrel implant insertion are rare and clinical consequences did not result in serious injury [66].

Removal

The rod can be removed at any time but should be removed when efficacy begins to decline (3 years after insertion according to the package insert; 5 years according to WHO studies). The hormonal effects end promptly after removal; circulating levels of etonogestrel are undetectable in 1 week. Return of ovulation occurs in 94% of women within 3–6 weeks after method discontinuation [34, 35]. If the implant is not removed at 3 years, contraceptive effects persist for at least an additional 2 years [39, 40].

Implant removal is an office procedure requiring only local anesthesia. Equipment is the same as that listed above for insertion, except that the Nexplanon applicator is replaced by sterile mosquito forceps (curved and straight) and a #11 scalpel. For removing deeply inserted implants, modified (<2 mm diameter ring) vasectomy forceps can be useful. Removal takes about 4 minutes [44] for Implanon and 2 minutes for Nexplanon [71]. Fibrous tissue surrounding Nexplanon is rare (4%) but increases removal time [44, 71]. Clinicians can view an instructional video and practice removal on a model arm before attempting the procedure on a patient. A removal kit containing a model arm and a manual and compact disc illustrating basic technique is available at no charge from Merck (by calling 877-467-5266). The patient should read and sign an informed consent, which is filed in her medical record. The patient also should be given a copy.

Procedure

Position the patient and prepare the implant site as described above for rod insertion. Some clinicians prefer that the patient extend her arm for the insertion procedure but bend her arm for implant removal.

Palpate the distal tip of the rod (the end closest to the elbow). If it is not palpable, then removal should be postponed until the rod can be localized with sonography or X-ray imaging combined with a referral to a provider with experience in removing non-palpable contraceptive implants. Push down on the proximal end of the rod (the end closest to the axilla) and inject no more than 0.5 mL of buffered lidocaine with epinephrine into the dermis immediately under the elevated distal tip of the rod, raising a wheal about 5 mm in diameter. Too much anesthetic, especially if it is injected on top of the rod, makes it difficult to palpate the tip of the rod. Massage this area to disperse the anesthetic.

Use your fingers to again apply pressure on the proximal (axillary) end of the rod so that the distal (elbow) end pushes up against the skin. As the rod is pushed against the skin, the blade of a #11 scalpel is positioned so that the point is immediately available to incise the sheath without releasing pressure on the rod. It is best to keep the scalpel in one hand with thumb and index finger while manipulating the rod with the rest of the fingers of both hands. Pushing the rod against the incision with finger pressure is critical for success with this "Pop Out" technique because, if pressure is released, the rod will slip back into its sheath in the subdermal tissue.

Make a 2–3 mm longitudinal incision through the skin over the end of the rod. Deepen the incision until you feel a rubbery sensation against the point of the scalpel blade; this is the rod encased in its fibrous sheath. Nick the fibrous sheath covering the end of the rod with the tip of the scalpel blade. It may take several nicks in different directions to fully open the sheath.

The end of the rod will come into view as the sheath is opened. Continue to exert finger pressure on the proximal (axillary) end of the rod to push the distal (elbow) end through the incision until it can be grasped with fingers or forceps and pulled out. Confirm that all 40 mm of the rod have been removed. Close the incision with an adhesive strip (e.g., butterfly bandage) and cover with a pressure bandage to minimize bruising.

Difficult Removals

If the rod will not move toward the incision with finger pressure, it can be grasped with a hemostat or modified vasectomy forcep (filed down to a 2 mm diameter grasping ring), but the incision will usually have to be lengthened in order to admit the clamp. It may be necessary to inject more local anesthetic, and to dissect around the rod with a straight mosquito clamp. The disadvantage of instrument removal is that it can be more painful, cause more bleeding, require a larger incision, and increase the risk of breaking the rod.

Once a rod is damaged, it can fracture with further attempts to grasp it with clamps. To decrease this risk, the rod should be grasped by its end whenever possible and with as little traction as possible for exposure and removal.

If it is not possible to grasp and push up on the end of a deeply implanted rod to open the fibrous sheath, use a scalpel to cut longitudinally, not across, the fibrous sheath covering the rod. Rarely, removal of a cut or broken rod will require an additional incision at the proximal end of the rod so that the remaining piece can be extracted. When the rod must be grasped around its diameter [a mid-implant removal], rather than at the end, the vasectomy forceps are particularly useful.

Rods too deeply placed cannot be palpated under the skin but can be seen with imaging studies (Implanon can be identified with high-resolution sonography or magnetic resonance imaging [MRI]; Nexplanon can be identified with high-resolution sonography, plain X-ray, computed tomography, or MRI). Such "lost" rods should be located with a high frequency (10–15 megahertz) linear ultrasound transducer prior to attempting the removal [72–74]. Use a transverse orientation to identify an acoustic shadow (the rod itself is more difficult to see), measure the depth, and draw a line representing the rod location on the surface of the skin. After making an incision, a straight hemostat clamp is used to divide the subcutaneous tissue until the level of the implant, as determined by the pre-procedure ultrasound study. The modified vasectomy clamp grasps around the implant and brings it to the skin surface. A scalpel is used to clear any overlying fibrotic tissue to free the implant for removal (Videos 7.1, Part 1 and 7.1, Part 2). If the rod is very deep (>1.5–2 cm), sonography should be used during the removal procedure because movement of the patient's arm may change the location of skin marks in relation to the underlying implant.

Patients with "very" (>2 cm) deep (as determined sonographically) implants should be referred to an experienced gynecologist. The contraceptive specialist can then work with interventional radiologists to remove the implant under direct imaging and controlled conditions. A case series of implant removal with a hook-wire marker method used in breast tumor surgery has been proposed [75] as has use of ultrasound with a modified vasectomy clamp [76].

Removal of contraceptive implants is *never* an emergency; there is no evidence that their presence adversely affects pregnancies or other conditions. Therefore, we suggest waiting until removal can be performed by a surgeon with expertise in removal of difficult contraceptive implants. Consultation with an orthopedic or plastic surgeon without specific expertise managing this problem is rarely required and not advised.

Reinsertion

If the patient wants to continue to use implant contraception, a new rod can be inserted immediately. If the previous implant was correctly positioned, the new implant can be placed through the same incision that was used to remove the old

rod. If the previous implant was placed in the biceps groove, the new implant should be placed in the updated insertion site (over the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the biceps groove). Alternatively, the new implant can be placed in the other arm.

Jadelle

Each Jadelle rod contains 75 mg of levonorgestrel for a total of 150 mg, 66 mg less than that in the six Norplant capsules [compared to 68 mg etonogestrel Nexplanon]. The thin, flexible Jadelle rods are wrapped in silastic tubing (the same material used by Norplant), 43 mm in length and 2.5 mm in diameter, thus slightly longer and thicker than Norplant [77]. Whereas the levonorgestrel in Norplant is packed into the capsules in crystal form, the core of the Jadelle rod is a mixture of levonorgestrel and an elastic polymer (dimethylsiloxane/methylvinylsiloxane). Long-term clinical trials indicate that the performance and side effects are similar to Norplant, but removal is faster [2, 78].

Because the release rates with the two levonorgestrel systems are comparable, it is reasonable to conclude that clinical studies with Norplant and Jadelle should yield similar results. While Norplant has been more extensively studied, clinicians can assume that the findings apply as well to Jadelle, except that Norplant was shown to be effective for 7 years and Jadelle for 5.

Summary

Implants offer women a highly effective, long-term, and easy-to-use method of contraception. They may be used in most women, including women with contraindications to estrogen, adolescents, women with chronic illnesses, and breastfeeding women. Implantable contraception is safe and cost-effective immediately post abortion and postpartum. Providers interested in placing and removing implants should undergo appropriate training, but all providers counseling women about contraception should be offered implantable contraception.

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Chapter 8
Intrauterine Contraception

Noa'a Shimoni, Ian J. Bishop, and Carolyn L. Westhoff

Types of Intrauterine Contraception

Women in the USA may choose among several types of intrauterine contraception (IUC):

- The CuT380A, a T-shaped polyethylene intrauterine device (IUD) with 380 mm^2 copper marketed as ParaGard®, approved for 10 years of use but provides effective contraception for as long as 12 years [1, 2], available in the USA since 1988.
- The LNG-52, a T-shaped polyethylene intrauterine system (IUS) that releases 20 μg of LNG/day, marketed as Mirena®, approved for 5 years of use, available since 2001. After 5 years, the device releases 14 μg LNG per day [3], which is sufficient for it to remain effective for at least two additional years [4, 5]. It is currently under study for use up to 8 years.
- The LNG-52, a T-shaped polyethylene IUS that releases LNG 20 μg/day, marketed as Liletta®, approved for 5 years of use, available since 2015 [6]. It is currently under study for up to 10 years of use.

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- The LNG-19.5, a T-shaped polyethylene IUS that releases LNG 18 μg/day, marketed as Kyleena®, approved for 5 years of use, available since 2016 [7].
- The LNG-13.5, a T-shaped polyethylene IUS that releases LNG 14 μg/day, marketed as Skyla®, approved for 3 years of use, available since 2013 [8].

General Overview of Methods

At the first peak of IUC popularity in the 1960s and 1970s, approximately 11% of contracepting women in the USA were using one of the many available IUCs [9]. After studies linked the Dalkon shield to septic abortion and serious pelvic infections, many US manufacturers withdrew their products from the market, and by 1988, only one IUC remained available in the US market [10].

Modern-day IUCs are safe and effective. In the world today, IUCs continue to be the most popular reversible method of contraception used by 14.3% of women [11]. Many different IUC products are available throughout the world. New types in trials today are likely to become available in the USA. A survey of 1552 members of the American College of Obstetricians and Gynecologists revealed that many members disregarded the evidence of safety regarding both adolescent and postabortion IUC placement [12].

All currently available devices offer effective, reversible, long-term contraception [13]. The copper and levonorgestrel IUCs each manifest a unique profile of benefits and side effects. Women using the copper IUD generally maintain their menstrual cycles but often experience increased menstrual bleeding. With the LNG-IUS, endometrial suppression results in an alteration of bleeding patterns and generally a reduction in bleeding; 20% of LNG-52 users, 12% of LNG-19.5 users, and 6% of LNG-13.5 IUS users will be amenorrheic within 1 year. By 5 years, 42% of LNG-52 users and 23% of LNG-19.5 users will be amenorrheic [6, 7].

Effectiveness

IUC devices are highly effective compared with other methods of contraception.

In the first year of use, the copper T380 IUD has a failure rate of 0.6% in perfect use and 0.8% in typical use. The cumulative failure rate for the copper IUD over 10 years of use is 2.1–2.8%. The first-year failure rate for the LNG-52 is 0.1% for both perfect and typical use. The cumulative failure rate is 0.7% over 5 years of use and 1.1% over 7 years of use. The UK National Institute for Health and Care Excellence reported a less than 10 in 1000 failure rates in 5 years for IUC [14]. The results of several studies consistently demonstrate that the failure rates of the CuT380A, LNG-52, LNG-19.5, and LNG-13.5 during typical use range from <1 to 1.4 pregnancies per 100 woman-years [3, 15–18].

Mechanism of Action

Experimental evidence suggests that IUCs affect events before fertilization and implantation [19, 20]. The primary mechanism of action for both copper- and LNG-containing devices is to prevent sperm from fertilizing ova [20, 21].

The majority of IUC antifertility actions occur before implantation. Copper ions in the IUD reduce sperm motility and viability so sperm rarely reach the fallopian tubes [21]. The CuT380A also increases white blood cells, enzymes, and prostaglandins in uterine fluids which primarily impair sperm function and secondarily inhibit implantation. The LNG-IUS inhibits fertilization by thickening cervical mucus and changing uterotubal fluid to impair sperm migration [22]. Secondarily, the IUS alters the endometrium to prevent implantation.

Advantages: Contraceptive-Linked Benefits

IUD as Emergency Contraception

Emergency insertion of the copper IUD within 5 days of unprotected sex is safe and is the most effective form of postcoital contraception in the USA [23]. The subsequent pregnancy rate in that cycle is 0.1% [24, 25]. The unintended pregnancy rate in women who received a CuT380A for emergency contraception (EC) at 1 year was half that of women who received oral LNG as EC [26]. A study of more than 1000 women who received a copper IUD for EC (including 170 nulliparous women) reported an overall pregnancy rate of 0.2% and continuation rates of 86% and 80% in parous and nulliparous women [27]. In an EC study that permitted women to choose a copper IUD or a combination of an LNG-IUS and oral LNG 1.5 mg, similar proportions continued to use the IUCs at 1 year (60% of CuT380A and 70% of LNG-IUS users) [28]. In a prospective cohort study of 180 women seeking EC, investigators offered all participants a copper IUD or an LNG-IUS with oral LNG. Study participants preferentially chose an LNG-IUS with oral LNG over a copper IUD; neither group had EC treatment failures [29]. Results are pending from a trial comparing LNG-IUS alone to ulipristal for EC [30].

Noncontraceptive Benefits: Therapeutic Uses of the LNG-52

Management of Heavy Menstrual Bleeding and Bleeding Disorders

The LNG-52 is as effective as medical or surgical management of menorrhagia or heavy menstrual bleeding.

All studies have documented an increase in blood hemoglobin and serum ferritin levels among users of the LNG-52, resulting from the inhibitory effects of the LNG-52 on the endometrium and the resulting decrease in menstrual blood loss [2, 31, 32]. This characteristic of the LNG-52 confers its therapeutic properties, and thus it can treat many common gynecological disorders including heavy menstrual bleeding [33, 34]. LNG-52 reduces menstrual blood loss in women with fibroids but does not reduce fibroid or uterine volume [35, 36].

Heavy menstrual bleeding, defined as menstruation of excessive flow and duration, is a common gynecological complaint and the most common cause of iron deficiency anemia. Studies have demonstrated a reduction in blood loss of up to 94% after 3 months of LNG-52 use and reductions of 79–96% after 12 months [31, 34, 37].

> Studies have compared the LNG-52 to oral or surgical management of heavy menstrual bleeding. In a study of 571 women with menorrhagia randomized to medical management or LNG-52 use, bleeding improvements in both groups were maintained over a 2-year period. The improvements in the LNG-52 group, however, were significantly greater than in the medical management group [38]. A Cochrane Collaboration systematic review concluded that the LNG-52 was more effective than oral therapy (progestins, combined contraceptives, mefenamic acid) for treatment of heavy menstrual bleeding with greater improvement in quality of life and greater continuation rates at 2 years [39].

Although both the LNG-IUS and endometrial destruction techniques reduce heavy menstrual bleeding, a Cochrane meta-analysis (of five randomized trials of low-quality evidence) reported that women who underwent endometrial destruction techniques subjectively reported a greater reduction in bleeding compared with the LNG-52 at 1 year [40]. Satisfaction at 2 years appeared comparable with the two treatments, and quality of life improved with either treatment. In Scandinavia, a randomized comparative trial of the LNG-52 versus transcervical endometrial resection in 60 women found similar reductions in both blood loss and number of bleeding or spotting days with the two treatments. Improvements in hemoglobin and serum ferritin concentrations were also comparable, but women treated with the LNG-52 reported less menstrual pain in the first 90 days after treatment than women in the resection group [31].

Management of Endometriosis

Endometriosis and Pelvic Pain

A few studies have demonstrated LNG-52 IUC effectiveness as a treatment for pelvic pain associated with endometriosis. A Brazilian clinical trial randomized 82 women with endometriosis-associated pelvic pain to treatment with either LNG-52 or the gonadotropin-releasing hormone (GnRH) analog, Lupron Depot®. Pelvic pain decreased equivalently in both groups and quality of life improved [41]. Another randomized clinical trial compared the LNG-52 to the etonogestrel implant in women with endometriosis-related pelvic pain. Both treatments significantly

improved pelvic pain and quality of life [42]. The LNG-52 can also be used in women with endometriosis for postoperative maintenance therapy; a meta-analysis showed comparable pain reduction with an LNG-52 or GnRH analog [43].

Additional observational studies confirm that LNG-52 use reduces pelvic pain and dyspareunia in women with endometriosis and can improve endometriosis stage with accompanying symptom reduction [44–46]. Studies of the LNG-52 in endometriosis patients have also demonstrated a decrease in extension of rectovaginal septum lesions as evaluated by ultrasonography and a decrease in the severity of lesions identified at laparoscopy [46]. The therapeutic effects of LNG-52 in endometriosis may be mediated through estrogen and progesterone receptors on endometriotic implants that are downregulated in the presence of LNG.

Management of Endometrial Hyperplasia

Progestin Therapy to Prevent or Treat Endometrial Hyperplasia

The LNG-52 is a means of delivering a potent progestin directly to the uterus for the treatment of endometrial hyperplasia. In a retrospective study of 32 women treated for complex atypical hyperplasia, grade 1 and 2 endometrial cancer with the LNG-52, 75% had partial or complete response at 6 months [47]. Endometrial hyperplasia may, however, recur after discontinuing the progestin [48, 49].

The LNG-52 is also used as an adjunct to estrogen therapy in menopausal women to protect against estrogen-mediated endometrial proliferation. Trials have demonstrated that LNG-releasing IUCs are effective and well tolerated in menopausal women receiving concomitant oral or transdermal estrogen therapy [50, 51]. In women taking tamoxifen for breast cancer, the LNG-52 reduced the incidence of benign endometrial polyps and endometrial hyperplasia [52].

Studies to date have found that IUD use is associated with a decreased risk for endometrial cancer [53]. Similarly, a systematic review and meta-analysis showed that invasive cervical cancer is about one-third less frequent in women who have used an IUD [54].

Clinical Considerations

Picking the Right Candidate

Good Candidates for IUC Use

IUCs are highly effective, safe, and reversible contraceptives with failure rates comparable to permanent contraception (e.g., tubal ligation) and contraceptive implants [55]. IUDs remain a relatively underused Tier 1 contraceptive method in the USA

often due to access barriers. IUC devices can be recommended for use among almost all women seeking a long-acting method including adolescents. The US Medical Eligibility Criteria, published by the CDC, includes recommendations for those with specific medical conditions and characteristics [56].

Especially Good Candidates for IUC:

- Women with medical conditions for whom pregnancy is dangerous
- Women who should not use an estrogen-containing contraceptive, such as those over 35 years of age with risk factors for cardiovascular disease, such as smoking, long-standing obesity, migraines with aura, diabetes, or history of thromboembolism
- Women using medications that induce liver enzymes (e.g., rifampicin, griseofulvin, phenytoin, carbamazepine, barbiturates, and primidone), as estrogen-containing contraceptives may be less effective in such women
- Women immediately after a vaginal or cesarean delivery (off-label) or first trimester/second trimester surgical abortion

Especially Good Candidates for Copper T IUD

- Postpartum women, breastfeeding or not, after 4 weeks or immediately after delivery of placenta (off-label)
- Women with contraindications to estrogen-containing contraceptives, for example:
  - Women with liver disease or hepatitis
  - Women with breast cancer
  - Women with hypertension or hyperlipidemia
  - Women with past/current ischemic heart disease, stroke, or multiple risk factors for cardiovascular disease
  - Women with uncomplicated valvular heart disease
  - Women with past or current deep vein thrombosis/pulmonary embolism
  - Women with migraines with or without focal neurological symptoms
  - Women with gall bladder disease or history of pregnancy-related cholestasis

Especially Good Candidates for LNG-52 IUS

- Women with heavy menstrual bleeding, dysmenorrhea, or endometriosis
- Women with bleeding disorders or on anticoagulation therapy
- Women with thalassemia, sickle cell disease, or iron deficiency anemia
- Women with endometrial hyperplasia

Poor Candidates for IUC Insertion

- Women with pelvic inflammatory disease (PID) within the last 3 months
- Women with purulent cervicitis or current gonorrhea/chlamydia
- Women with pelvic tuberculosis
- Women with recent septic abortion or puerperal sepsis
- Women with uterine abnormalities or fibroids distorting the endometrial cavity

- Women with undiagnosed genital bleeding
- Women with allergy to any component of the IUD
- Women with Wilson's disease (copper IUD only)

Infection

Routine antibiotic prophylaxis is not recommended before IUC insertion [57]. A 1999 meta-analysis of randomized controlled trials showed antibiotic prophylaxis at time of IUC insertion did not decrease PID risk nor did it reduce the odds of IUC removal within the first three months [58].

Women who have not received routine screening for STIs or have been identified at increased risk for STIs based on history should receive CDC-recommended STI screening at the time of IUC insertion. Do not delay IUC insertion while awaiting test results; treatment for a positive test result can occur without IUC removal [57].

If a genital tract infection is suspected after IUC insertion, administer antibiotics promptly to the patient and partner per CDC guidelines. The patient may retain the IUC if desired [56]. A randomized controlled trial showed no added benefit to IUC removal during treatment for acute salpingitis [59].

Actinomyces species are regarded as normal inhabitants of the female genital tract, and presence on a pap smear is not a harbinger of pelvic infection nor does it require antimicrobial treatment [5, 60]. Higher rates of *Actinomyces*-like organisms in the pap smears of IUC users were found among copper IUD compared with LNG-20 users [61]. Asymptomatic women with an incidental finding of *Actinomyces* colonization can be informed of the result and can continue IUC use. If the infection is symptomatic, then remove the IUC promptly, send cultures, and begin long-course antibiotic treatment.

Ectopic Pregnancy and IUC

The IUC is effective at preventing both intrauterine and ectopic pregnancies [1, 4, 6–8]. Women using an IUC have a lower incidence of ectopic pregnancy than non-contracepting women because the IUC is a highly effective method of contraception and prevents all types of pregnancies. Copper T IUD users have approximately one-half the absolute risk of ectopic pregnancy than women who are not using any type of contraception [3, 62].

When pregnancy is suspected in an IUC user, an ultrasound is required to rule out an ectopic pregnancy. Among IUC users with contraceptive failure, the risk of ectopic pregnancy is high. In a case–control study, women diagnosed with an ectopic pregnancy were 16 times more likely to be currently using IUC than women diagnosed with an intrauterine pregnancy [63]. The rate of ectopic pregnancy with

a copper-bearing IUD is 0.09 per 100 women at 1 year [64]. Ectopic pregnancy rate among LNG-52 users is 0.045 per 100 women at 1 year [62]. The rate of ectopic pregnancy in women not using any contraceptive is far higher than that seen in women using IUC [65, 66].

Fertility Post-IUC

Fertility returns promptly after removal of either the copper T IUD or the LNG-52 IUS. Previous retrospective studies incorrectly concluded that IUC use was a cause of elevated rates of PID and subsequent infertility [61, 67]. In a case–control study of nulliparous IUC users, tubal infertility was correlated with the presence of *Chlamydia* antibodies, not the IUC [68]. Among 110 women who discontinued using these methods to become pregnant, more than 90% in both groups conceived within 1 year [69, 70]. A systematic review revealed that the 1-year pregnancy rate for women who discontinue either IUC is similar to the rate in women who discontinued barrier methods or used no contraceptive method [71].

Insertion and Removal

Insurance

Following passage of the Affordable Care Act, many insurance companies fully cover the cost of IUC insertion as preventive care. Clinical practices may choose to stock devices and bill the patient's insurance (buy and bill). Or clinicians can order a device for each patient individually through online pharmacies that verify benefits, bill insurance, and then dispense the IUC to the practice. Some insurances require buy and bill, which has benefits and drawbacks. With buy and bill, patients are more likely to receive same-day devices, but practices have greater upfront costs.

Initiation Timing

IUC devices may be placed anytime with reasonable assurance that the patient is not pregnant, for example, on days 1–7 of the cycle or if switching from another highly effective method of birth control. Insertion during menses provides additional evidence that the patient is not pregnant. The CDC's Selected Practice Recommendations (SPRs) provide clinicians with a six-item checklist of how to be reasonably certain that a woman is not pregnant [72]. These criteria are strict, and women may be turned away from same-day insertion. In the Contraceptive CHOICE Project, 31%

(n = 2158) of women seeking contraception did not meet pregnancy checklist criteria; they were offered less effective interim contraception and scheduled for later insertion [73].

Same-day insertion may still be appropriate for patients with a negative urine pregnancy test even when SPR criteria are not met. The small risk of an undetected luteal pregnancy (early pregnancy when a urine test is not yet positive) should be discussed with the patient, and shared decision-making will inform if same-day placement is appropriate. In the Contraceptive CHOICE Project, the rate of luteal-phase pregnancy was 0.5% in women with a negative pregnancy test [73].

If the IUC is inserted more than 7 days after menses started, the patient should be instructed to use a backup method or abstain for 7 days [72]. Postpartum or postabortion initiation is discussed below.

Insertion Tips and Techniques

Because devices vary in size, shape, inserter mechanism, and insertion technique, providers must follow manufacturer instructions. A bimanual pelvic exam is needed to assess the size, shape, and position of the uterus and to exclude signs of pelvic infection. Sterile gloves should be used to load the CuT380A or to touch any part of the inserter tube that will enter the uterus. Alternatively, the CuT380A may also be loaded without sterile gloves through a partially opened sterile package [95].

Although widely used, numerous studies agree that pre-procedure nonsteroidal anti-inflammatory drugs (NSAIDs) do not reduce insertion pain, nor do intracervical lidocaine gel or misoprostol [74, 75]. However, NSAIDs administered an hour before IUC insertion appear to improve post-insertion pain [76].

> Paracervical blocks are promising for decreasing pain with insertion. Two recent studies of nulliparous women who received a 1% lidocaine paracervical block demonstrated decreased pain during IUC insertion [77, 78].

Check individual IUC package inserts for full instructions. “No touch” procedures are required.

The basic technique for all IUC insertions is as follows:

- Perform pre-insertion pelvic exam to accurately locate position of uterus.
- Place an adjustable speculum.
- Collect gonorrhea/chlamydia specimen, if appropriate.
- Apply antiseptic such as iodine or chlorhexidine to cervix.
- Administer a paracervical block if desired.
- Apply tenaculum and pull gently to straighten the angle between the cervix and uterus in order to reduce perforation risk and suboptimal IUC placement.

- Sound the uterus to confirm uterine position, identify any intrauterine anomaly, and measure uterine depth in centimeters [usually 6–9 cm for copper IUD; greater depth acceptable for LNG-IUS or if patient is postpartum or postabortion].
- Open the IUC package once sounding is successful.
- Proceed with manufacturer's instructions to load and place the device.
- Cut strings, typically to 3 cm.

Removal Tips

Slow steady traction on the IUC strings with ring forceps will facilitate easy removal. Application of a tenaculum to straighten the axis of the uterus may be useful, especially with marked flexion of the uterus. If the strings are not visible, gently probing inside the cervical canal with a cytobrush can often find the wayward strings. Confirm the IUC is intrauterine by ultrasound before proceeding further. Then consider an IUC hook, alligator forceps, metal pipelle, or manual vacuum aspiration with a small cannula to remove the device. Liberal use of paracervical local anesthesia for patient comfort may be helpful if cervical dilation or uterine exploration is required for IUC removal. Rarely, hysteroscopy is necessary for removal.

Counseling Tips

- Use of NSAIDs (e.g., 600–800 mg ibuprofen) 1 hour before insertion may help to ease pain later that day after insertion.
- Following painful insertions, redosing the NSAID until bedtime may be very helpful (and may avoid a call back to the office).
- Although not required, the patient can be instructed on how to feel for the IUC strings. This allows the patient to assess IUC presence without depending on the provider and may be reassuring.
- After insertion, routine string check visits are not necessary. A checkup 6–8 weeks post-insertion may be appropriate in order to address concerns, assess satisfaction, and normalize common side effects like bleeding and spotting. Routine ultrasound is not needed.
- A woman is unable to feel her strings, she should return to the clinic and use backup protection in the meantime.
- Spotting, bleeding, and cramping are common in the first 90 days of IUC use.
  - Either heavy menstrual flow, intermittent bleeding, or spotting may occur with the CuT380A.
  - Decreased menstrual flow or amenorrhea may occur 3–4 months after LNG-IUS insertion.

- Use of anti-inflammatory medications to control bleeding or pain, especially during the first months of use, may help promote continued use.
- As with all forms of contraception, users who may be exposed to sexually transmitted infections should also use a condom.
- Women using a CuT380A should have a pregnancy test if they miss a period. A pregnancy test should also be done in women with an LNG-52 following a dramatic change in bleeding pattern.
- The Food and Drug Administration recommends that the IUC be removed if a user becomes pregnant, if it can be removed easily and without an invasive procedure.
- The IUC should be removed after menopause unless the patient is using the LNG-52 as an adjunct to estrogen replacement therapy. Waiting for 1 year of amenorrhea or checking markers of ovarian reserve (to ensure menopausal status) before removing the device may be appropriate.

Management After Placement

Expulsion

Expulsion is the passage of IUC either partially or completely though the internal cervical os. The symptoms of IUC expulsion include cramping/pain, unusual vaginal discharge, dyspareunia, postcoital spotting, and presence of the IUS plastic in the cervical os or vagina. Reported first-year expulsion rates range from 2% to 10% and vary by IUD type [79].

> A secondary analysis further investigated whether age and nulliparity are associated with expulsion of an LNG-IUS or copper IUD. IUS expulsions were not increased in nulliparous females. However, more expulsions were observed in females aged 14–19 compared with older women, after controlling for parity or IUD type [80].

Women who expel one IUC have a one in three chance of expelling a subsequent IUS [81]. Reinsertion of a new IUC following expulsion is acceptable, but there are limited data regarding management of repeat expulsions. Studies are ongoing to determine safety of the use of a menstrual cup with an IUS [82].

Provider experience may play a role in expulsion. In a multinational study of post-placental insertion after vaginal delivery, pooled data from all sites showed that insertions performed in the first half of the trial, when investigators had little prior experience, were associated with higher expulsion rates than insertions in the second half (12% vs. 7%, $p < 0.001$) [83].

In a systematic review and meta-analysis, postpartum IUS expulsion rates varied by insertion timing, delivery method, and IUS type. Immediate and early postpartum placements were associated with increased risk of expulsion compared with interval placement. Pooled expulsion rates varied by insertion timing and ranged from 1.9% with interval placement (4 weeks or more postpartum), 10% for immediate placement

(up to 10 minutes after placental delivery via either cesarean section or vaginal delivery), and 29.7% for early placement (between 10 minutes and 4 weeks postpartum). Early postpartum placement after vaginal delivery was associated with an increased risk of expulsion compared with cesarean delivery. The LNG-IUS was also associated with a higher risk of expulsion compared with the CuT380A [84].

Perforation

Uterine perforation with IUC insertion is rare. In a cohort study of over 60,000 women, overall perforation rates (by 5 years) were slightly higher in LNG-52 users than copper IUD users (2.1 and 1.6 per 1000 insertions). Breastfeeding was a significant risk factor for perforation, which was further increased in women who had IUC inserted within nine months of a delivery. In this study, perforations did not lead to serious illness or to injury of intra-abdominal or pelvic structures. In the small number of perforations identified, over two-thirds were associated with previously suspected risk factors (e.g., breastfeeding) [85].

> Small trials and observational studies of post-placental insertion suggest that perforation is similarly rare. In a prospective study of 8343 women who received a CuT380A at different postpartum timings, there was only one documented perforation among 460 post-placental insertions (0.2%). This risk was similar to the risk of interval insertion more than 6 months after delivery [86].

Bleeding and Pain

While most women note a reduction in irregular bleeding and cramping with an IUS over time, some may experience patterns of continued bleeding and cramping that vary by IUS type and progestin amount. Greater LNG content in an IUS is more likely to inhibit bleeding and spotting and more likely to result in amenorrhea [18, 87, 88]. Copper IUDs are commonly associated with increased menstrual bleeding. In one study, the rate of copper IUD removal for reports of pain and bleeding was higher than for the LNG-IUS [89]. Women who continue to have ongoing heavy bleeding and cramping three months or more after insertion should be evaluated with the same workup as would be done in non-IUD users keeping in mind that the differential diagnosis remains similar and includes pregnancy, endometritis, or polyp. A small pipelle endometrial biopsy can be considered to rule out malignancy (and the IUC can remain in place).

Pre-insertion counseling and post-insertion reassurance are frequently the only interventions needed for bleeding and cramping in the first months after IUC insertion. If bleeding and/or cramping persists, begin with a short (5–7 day) course of NSAIDs like ibuprofen 800 mg every 8 hours or naproxen 500 mg twice a day. If bleeding persists, consider a 3-month trial of combined hormonal contraception or progestin-only contraceptives.

Imaging

Using sonography may sometimes be helpful to guide IUC placement. In the setting of a markedly ante- or retro-flexed uterus, multiple cesarean sections that may have kinked the cervical canal, or significant obesity that can make a bimanual exam uninformative regarding uterine position, IUC placement can be more difficult. When these conditions are present, transabdominal sonography during sounding and IUC placement can help achieve successful insertion and reassure both the clinician and the patient about the IUC position. If during an insertion attempt the direction or depth of the sound is not compatible with the previous bimanual examination, the sound may have perforated the uterus, and using sonographic guidance to continue the insertion may be prudent. Finally, if a patient reports unusually severe pain during or after placement, sonography can assist in evaluating for IUC position and signs of perforation. Bear in mind, however, that perforation occurs during only 1–2/1000 insertions and is often asymptomatic.

Routine imaging during or after IUC placement is not necessary. Using sonography to check the IUC position during its many years of use is simply not needed. If the string is present, one should assume the IUC is correctly located without imaging. Studies of routine serial imaging have shown that IUCs move down and up again within the uterine cavity over time [90]. Changes in device position are not clinically important if the device remains fully within the cavity. Managing patients should be based on symptoms and not on IUD position: Reporting that an IUC is "low" in the uterus is not clinically important as long as the device is above the internal cervical os.

> If a patient is asymptomatic and the string is visible, do no imaging. If a patient has worsening symptoms (such as pain and bleeding) during IUC use, then manage primarily based on the symptoms.

Missing Strings and Retained IUC

IUC strings are sometimes drawn into the uterine cavity and thus not visible or palpable. This is usually harmless but requires confirmation of the IUC position because either perforation or an unnoticed expulsion may have occurred. If exploring the cervical canal (for instance, using a cytobrush) does not yield the missing strings, sonography to check for IUC position should be the next step. If sonography reveals no IUC within the uterus, further imaging should look for the IUC in the abdominopelvic cavity. A flat plate X-ray of the abdomen is suitable for the purpose. In the case of a hormonal IUS, measuring LNG concentrations will reveal if the device is still in the woman's body. If the IUC is found outside the uterine cavity, it will require removal via laparoscopy.

If the strings are absent or if traction does not bring the IUD into the vagina, additional measures are needed. Inserting an IUC hook, metal pipelle, or narrow alligator forceps often retrieves the IUC even without the help of imaging. Using a paracervical block, tenaculum placement to straighten the cervix, and modest cervical dilation (to 5 or 6 mm) will facilitate this. When using these maneuvers, however, many clinicians will appreciate using sonography to localize the IUC within the cavity and make the retrieval quicker and easier. If using forceps under sonographic guidance is insufficient to grasp and remove the IUC, hysteroscopy is useful because it is possible that a portion of the IUC has become embedded in the uterine wall. Embedment is more likely with IUCs that have been in place for many years or when a woman has developed leiomyomata while using the IUC. Office-based hysteroscopy is usually successful. If the IUC is firmly embedded, then one needs to consider using sedation for patient comfort. Removal of a firmly embedded IUD may leave a fragment behind – leaving an IUC fragment in situ seems to be harmless, but the natural history is not well described. Common sense suggests that an experienced hysteroscopist will have greatest success in removing an embedded IUC.

Special Populations

Postabortion

Placement of IUC at the time of induced or spontaneous abortion is safe [91]. Ovulation can occur as early as 10 days after abortion, so women who have an abortion are at high risk of pregnancy immediately after and may benefit from early initiation of contraception [92]. One study reported that women who chose to have IUC placed immediately following an abortion used those devices at higher rates than those who chose interval insertion and women undergoing immediate postabortion IUS insertions had lower rates of subsequent abortion than those who chose short-acting contraceptive methods [93]. Women choosing immediate postabortion IUC insertion have high rates of continuation and satisfaction (6-month continuation rate was 78.6% and satisfaction rate was 85.2%) [94].

Nulliparity

Providers may be concerned about IUC complications, such as pain and difficulty with insertion in nulliparous women, and this may limit their willingness to recommend IUC to nulliparous women. Evidence suggests, however, that complications are rare. In a large study of adolescents, first-attempt insertion was successful 95.8% of the time with similar rates between the nulliparous and parous cohorts [95]. IUC expulsions are not increased in nulliparous women, but rather

more expulsions have been observed in females aged 14–19 compared to older women regardless of parity of IUC type [80, 96].

IUC should be offered to nulliparous women as a safe and effective contraceptive option. The US MEC classifies IUC use in nulliparous women as category 2 (advantages of using the method generally outweigh the risks) [56]. Product labeling for IUC in the USA no longer contains language to discourage placement for nulliparous women [14]. Satisfaction and continuation rates remain high for nulliparous women [97].

HIV

The US MEC 2016 has classified IUC insertion for HIV-positive women who are clinically well receiving antiretroviral (ARV) therapy as a category 1, whereby there is no restriction (method can be used) [56]. Those not clinically well or not receiving ARV therapy are classified as category 2 (advantages generally outweigh theoretical or proven risks). IUCs do not have clinically meaningful drug interactions with antiretroviral medications [98]. Limited evidence shows a low risk for PID among HIV-infected women using IUCs and no higher risk of pelvic infectious complications in HIV-infected than in HIV-uninfected women or among women with varying degrees of HIV severity. IUC use did not adversely affect progression of HIV during 6–45 months of follow-up or when compared with hormonal contraceptive use among HIV-infected women. Furthermore, IUC use among HIV-infected women was not associated with increased risk for transmission to sex partners or with increased genital viral shedding [99, 100].

> The multicountry randomized ECHO (Evidence for Contraceptive Options and HIV Outcomes) Trial Consortium measured HIV incidence among women assigned to one of three highly effective contraceptive methods and did not find an increased susceptibility to HIV acquisition among women using the copper IUD [101]. As with anyone with a sexually transmittable illness, regardless of contraceptive method chosen, a barrier method should be promoted to reduce transmission.

Future Devices

IUCs are categorized as drugs rather than devices in the USA. Since drugs are approved by the Food and Drug Administration through an arduous and expensive process, limited types of IUCs are available in the USA compared with other counties. The goals of new devices in development are to minimize side effects such as bleeding, spotting, and pain and to accommodate a smaller uterus. LevoCept and VeraCept, two devices in phase 3 clinical preapproval trials, are composed of a flexible nickel/titanium wire frame that supports either LNG or copper. Their frame is distinct from the polyethylene T-shaped frame of IUCs currently available in the USA. A smaller copper IUD is also under clinical trials in the USA.

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Chapter 9
Barrier Contraceptives

Robyn Schickler and Jasmine Patel

Introduction

The history of barrier contraceptives has been long, with changes and developments along the way meant to improve the available methods. External condoms, traditionally referred to as male condoms, are now made with several different materials, providing an option for those with latex allergies and with added features (e.g., thinner, colors, flavored) to make their use more appealing. The internal condom, or single-use female condom, is now made from nitrile, a less costly material than the polyurethane from which it was previously made; however, the cost can still be prohibitive without a prescription.

The traditional contraceptive diaphragm has also had limited popularity and availability. However, the Caya® diaphragm, created to fit the female anatomy as a "one size fits most" device, was approved for use in the United States in 2014. The Caya® diaphragm does require a prescription, but no fitting is necessary and the patient obtains the diaphragm online. If the Caya® diaphragm is not appropriate for a woman, the appropriate fitting diaphragm needs to be directly provided or sold to the patient from the provider or clinic. The Femcap®, which is the currently available cervical cap in the United States, requires a prescription and is available at limited participating pharmacies but otherwise is purchased online.

The Today® contraceptive sponge can be purchased over the counter, but stores may not always have a consistent supply available. The only currently available

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vaginal spermicide is nonoxynol-9, which unfortunately can be abrasive and irritating to the vaginal and cervical mucosa. Per the 2016 CDC Medical Eligibility Criteria, nonoxynol-9 use is contraindicated in women at high risk of HIV [1] due to the concern for increased risk of transmission [2]. The barrier methods have some of the highest failure rates; emergency contraception should therefore be offered and prescribed prophylactically for patients using these methods.

Each barrier method has its own advantages and disadvantages, but some are shared between all or some of the barrier methods. Additional advantages or disadvantages of each method are described in that method's section later in this chapter.

Advantages of Barrier Methods as a Group

- Alternative to hormonal methods of contraception.
- Used only with coitus.
- Portable.
- Immediately reversible.
- May be combined with a more effective hormonal method to enhance efficacy or use for noncontraceptive benefits.
- Except for combining an internal condom and external condom, the barrier methods may be combined with other barrier contraceptives to enhance efficacy or provide STI protection.
- Vaginal barrier methods are controlled by the woman and therefore are less dependent on male involvement.

Disadvantage of Barrier Methods as a Group

- User dependent.
- Required with every act of coitus.
- Higher failure rates.
- May require negotiating with partner and therefore more subject to sabotage.
- The internal condom, diaphragm, and cervical cap all require advanced planning prior to coitus (Table 9.1).

External (Male) Condoms

The external condom is a physical barrier that covers the glans and the shaft of the penis, applied prior to intercourse. External condoms trap ejaculate and earlier secretions and thus provide STI protection in addition to contraception. External condoms may also be used off-label for STI protection during oral and anal

Table 9.1 First-year failure rates of barrier contraceptives

	Correct and consistent use	Typical use
External condom	2%	13%
Internal condom	5%	21%
Female cervical cap	13.5% at 6 months	Not rated
Contraceptive diaphragm	6–12.5%	12–18%
Contraceptive sponge		
Parous women	20%	29%
Nulliparous women	9%	12%
Vaginal spermicide	18%	28%

Adapted from Trussel, J. *Contraceptive technology*, 21st ed. [Permission obtained from Executive Editor of *contraceptive technology*, 21st ed.]

intercourse. Most condoms are 7 inches in length, 2 inches in width, and 0.07 mm (0.003 inches) thick. However, studies show that 20–30% of men cannot use these condoms; there are size variations to provide a better fit for a greater number of men. ONE® condoms have created 60 different condom sizes based on penile measurements that can be ordered and purchased online.

External condoms are made with a variety of different materials, each having different properties. Latex condoms are the most commonly used and most studied condom material. The latex condom significantly reduces the spread of most STIs including chlamydia, gonorrhea, HIV, hepatitis B, and trichomonas. Latex condoms come in a variety of designs: some have a reservoir at the tip, while others are flat tipped and require the user to leave space at the end in order to collect ejaculate. There are condoms that are the same diameter from tip to base, while others flare at the end, over the glans. Latex condoms can feel cold as they do not transmit body heat. Additionally, latex allergies occur in an average of 4.3% of the general population worldwide, and thus latex is not an appropriate material for use in these couples. Latex condoms cannot be used with oil-based lubricants, such as baby oil, lotion, or petroleum jelly, as the oil causes breakdown and eventual damage to the latex condom.

An alternative material to the latex condom is the plastic condom, made with either polyurethane or polyisoprene. Plastic condoms do not stretch like latex and so are made only in larger sizes. Polyurethane can be used with an oil-based lubricant, but the material does lend to breakage more easily than latex. Polyisoprene is a synthetic form of latex without the allergenic latex allergens; like latex condoms, oil-based lubricants should not be used with polyisoprene condoms. Unlike latex, plastic condoms do transmit body heat. The pores are small enough in plastic condoms to provide protection against the smallest sexually transmitted viruses.

Another material used in nonlatex condoms is marketed under the name "lambskin," although the material is made from lamb cecum. This was previously the only alternative for those with latex allergies to provide some protection from pregnancy and STIs. However, the pores in the material are relatively large and do allow for passage of smaller viral STIs, and those with latex allergies have better options for condoms today.

Some latex condoms are coated with nonoxynol-9 spermicide to provide better protection; however, the use of spermicide does not increase pregnancy protection, nor does it prevent or reduce the risk of HIV or other STIs. The FDA has a warning label on over-the-counter spermicides indicating that it does not protect against HIV or STIs [3] and that the spermicide may increase the risk of HIV transmission secondary to mucosal damage and irritation [2].

Efficacy

External condoms have a perfect use failure rate of 2% [4] and a typical use failure rate of 12.6% [5] during the first year [4]. The male condom is a commonly used contraceptive method with 93% of women having ever used the method [6]. Approximately 24% of women and 34% of men report male condom use in the prior year [5]. In adolescents, approximately 54% of sexually active teenagers report use of a male condom during their last act of intercourse [7]. In those who choose condoms for their contraceptive method of choice, when given free supplies, 56% consistently used condoms with every episode of intercourse in the prior 14 days; the most common reason for nonuse was the thought that the woman was not at risk of becoming pregnant, followed by having run out of or not having supply available [8]. Randomized trials have shown that up to a third of cycles are not adequately protected from pregnancy due to condom nonuse [9]. The clinical breakage and slippage rates of the external latex condom are each approximately 2% [10]. A condom that does not properly fit can contribute to slippage and breakage as it may be too loose or tight around the penis. It is important for patients to find an appropriately sized condom to avoid condom failure. ONE® condoms provide "perfect-fit" condoms that can be ordered at an online website where a recommendation for appropriate condom size is made based on penile measurements [11].

Mechanism of Action

The external condom, which covers the glans and shaft of the penis, acts as a physical barrier that prevents semen from entering the vagina, thereby reducing the risk of pregnancy. The condom also reduces the risk of STI transmission by covering the mucosal surfaces that allow for transmission of these infections.

Advantages of External Condoms

- Low failure rate when used correctly and consistently.
- Few contraindications to use.

- Protects against STIs, reducing risk of transmission of HIV, gonorrhea, chlamydia, syphilis, trichomonas, herpes simplex virus (HSV), and human papilloma virus (HPV).
- There are no systemic side effects, except in cases of allergic reactions to latex.
- Can be purchased over the counter, without prescription.
- Latex is a renewable resource.

Disadvantages of External Condoms

- Requires male cooperation.
- May disrupt sexual pleasure.
- Possible erection loss [12].
- Latex allergy affects an average of 4.3% of the general population.
- Man may have difficulty achieving orgasm [13].
- Possible decreased sensation [14].
- Condom package may be difficult to open.
- User must avoid petroleum or oil-based lubricants.
- Latex odor and/or taste can be unappealing.
- Possible perceived wastefulness and environmental impacts of single-use condom.
- Some women experience pain with male condom [15].
- Need to withdraw penis immediately following ejaculation, even if partner has not achieved orgasm.
- Concerns about trust may arise when one partner requests condom use.

Instructions for Correct Use [16]

- Encourage discussion between patient and partner prior to coital acts that a condom will be used.
- Use condom with every sexual act.
- Use a new condom for any new mucosal contact (vagina, oral, anal).
- Select appropriate size and style and ensure that the condom is good quality. Make sure there are no defects or holes in the condom and check the expiration date.
- Store at room temperature.
- Use water- or silicone-based lubricants only. Do *not* use oil-based products as these can damage latex condoms [17].
- Handle with care; do not use any sharp objects to open the package and be wary of genital piercings.
- Place fresh condom on the head of an erect or semi-erect penis. If the penis is uncircumcised, the foreskin should first be pulled back before condom applica-

tion. Pinch air out of the tip and roll down completely over the shaft of the penis. Keep condom on the penis until after intercourse.
- After sex, but prior to withdrawing, hold the condom at the base to keep in place, and then withdraw the penis. Once withdrawn, remove the condom. Inspect the condom for any damage, tears, or breaks. Wrap in tissue and throw in the trash; do not flush down toilet.
- If the condom breaks or slips during sex, remove the penis immediately. The woman may place spermicidal foam immediately and/or use emergency contraception. If at risk, both partners should consider the need for STI prophylaxis.
- Discard condom after each use, and do not reuse condoms.

Patient Counseling

- Discuss the signs and symptoms of latex sensitivity/allergy, and make sure to discuss nonlatex condom availability.
- Emphasize correct and consistent use for STI protection and pregnancy prevention if applicable. May need to explain the difference between typical use and perfect use failure rates.
- Remind patient to use a new condom with any new mucosal contact (e.g., switching from oral to genital).
- Encourage dual use of condoms with a first- or second-tier contraceptive method to provide both effective pregnancy prevention and STI protection. Also consider use with another barrier method (except for internal condom) or with fertility awareness methods especially during pregnancy risk days.
- Discuss how patient may negotiate condom use if he or she is uncomfortable suggesting this to their partner. If there is concern for intimate partner violence, refer as appropriate.
- Discuss choice in condom styles that would be suitable for the patient and partner, such as the desire for increased sensation with a vibrating ring or ribbed condom, the need for different size of condom, or flavored condoms.
- Provide condoms directly or resources for provision, especially if patient is embarrassed to purchase in the store. In these cases, discuss the availability of condoms online.

Future Developments

Newer condoms are in development, including the Origami condom, which opens when the penis enters the vagina, rather than requiring the user to roll down over the shaft. The Galactic Cap design covers just the glans penis rather than the entire shaft, meant for couples at low risk for STIs but who need more stimulation. The hydrogel condom is being developed as a nonlatex alternative that simulates the tactile sensation of skin better than a latex condom. One-handed condom wrappers allow for an easier-to-open package for less disruption. Currently available

"Wingman" condoms were developed to more easily roll down the penis and are heat-sensitive and able to conform to the shape of the penis.

Vaginal Barriers

Table 9.2 shows each of the available vaginal barriers and provides descriptions of the methods. In general, women who use vaginal barriers must be willing and able to touch their genitalia. Vaginal barriers should not be used during menses for

Table 9.2 Vaginal barrier methods

Device	Description	Mechanism	Failure rates with		Availability
			correct/ consistent use	Typical use	
FC2® (internal condom)	Nitrile sheath with flexible inner ring at top of vaginal vault and outer ring at introitus	Barrier	5%	21%	Over the counter, free with prescription (unless copay required)
Caya® (contraceptive diaphragm)	Silicone dome-shaped device that covers cervix	Barrier and spermicide	6–12.5%	12–18%	Sized by obstetric history Requires prescription or direct provision by clinician Caya® available online and OTC
FemCap® (cervical cap)	Silicone cap that covers cervix, shaped like sailor's hat	Barrier and spermicide	13.5% at 6 months	Not rated	Over the counter Available online Sized by obstetric history
Today® (contraceptive sponge)	Soft polyurethane sponge with 1 g N9, concave indentation that covers cervix	Spermicide Some barrier mechanism	Nulliparous: 9% Parous: 20%	Nulliparous: 12% Parous: 29%	Over the counter Failure rate higher in parous women
Spermicides	Nonoxynol-9 in the form of foams, gels, films, suppositories	Spermicide	18%	28%	Over the counter May increase risk of HIV transmission

prolonged periods due to the increased risk of toxic shock syndrome, and most barrier devices, except the internal condom, must be left in place for at least 6 hours after intercourse.

Internal (Female) Condoms

The internal condom currently available in the United States is the FC2®, a synthetic nitrile sheath coated in silicone-based lubricant, 17 cm in length, and 7.8 cm in diameter. The condom contains a larger nitrile ring at the base that sits at the introitus and covers the vulva. A smaller, inner ring made of polyurethane within the condom at the closed end sits at the top of the vaginal vault. Once in the vagina, the inner ring rotates parallel to the top of the vault, thereby stabilizing its position. The internal condom is less likely to break than the external latex condom [18]. Additionally, the internal condom is FDA approved for STI protection with anal intercourse. The FDA changed the name of the female condom to "single-use internal condom" to degender the product, given its approval for both vaginal and anal intercourse. The condom was also downgraded to a Class II medical device, which eases the burden on manufacturers to obtain FDA approval for newer or updated products.

Efficacy

The internal condom has a first-year failure rate of 5% with perfect use and 21% with "typical use" or the calculated 12-month pregnancy rate in clinical trials. This large difference in perfect use and typical use failure rates may reflect difficulty in correct use. Correct use requires involvement from both partners, the condom must be in place prior to any genital contact, and the penis must be placed directly into the vagina. The outer ring must be stabilized during intercourse to prevent invagination of the condom during sex, which would allow mucosal contact. Failure does decrease with greater user experience, particularly after the first five uses [19].

Vaginal spermicides may be used with the internal condom to provide additional protection. However, internal condoms should never be used with an external condom.

Mechanism of Action

The internal condom acts as a physical barrier and traps ejaculate, thereby preventing it from entering the female upper genital tract.

Advantages

- Protects from pregnancy and from STIs; also protects the penis and part of the testicles from contact with the vulva, reducing transmission of infection from skin contact.
- Can be placed up to 8 hours prior to intercourse; if placed early, does not interrupt intercourse.
- Available over the counter, may be free with prescription or require copay.
- Can be used in those with latex allergies.
- In comparison to external condoms, the internal condom does not decrease sensation to the same extent, and the outer ring may enhance pleasure.
- Does not require male erection to be maintained, nor does it require withdrawal immediately after ejaculation.
- Warms to body temperature.

Disadvantages

- Expensive, unless a prescription is obtained.
- Correct use can be difficult.
- If used incorrectly, the condom can slip into the vagina and expose mucosa to semen.
- Nitrile sheath can sometimes be irritating to the vulva and/or vagina.
- Tears may occur if genital jewelry present.

Instructions for Correct Use [20]

- Use with every act of intercourse.
- To open the packet, identify the arrow and tear from the notch at the top of the package. Do not use a sharp object to open package to avoid tears or breaks in the condom.
- Hold condom at the closed end with the flexible inner ring, allowing the larger outer ring to hang down. The condom's inner ring is then compressed between the middle finger and thumb.
- The inner ring may then be introduced into the vagina. The woman may position herself by squatting, raising one leg, sitting, or lying down. With her fingers inside the condom, she should then push the inner ring upward into the vagina, as far as it will go near the pubic bone. The outer ring should remain outside the vagina.

- When intercourse begins, the partner's penis should be guided into the vagina. If there is any discomfort once the penis is inside, the inner ring may need to be adjusted.
- After intercourse, remove the condom by twisting the outer ring and gently pulling. Wrap in a tissue and throw into garbage. Do not flush down toilet.

Patient Counseling

- Patient should not wait until the last minute to apply condom. It should be placed early in anticipation of intercourse, which can help avoid problems with insertion difficulties and slipping.

Future Developments

Other internal condom designs (not available in the United States) include:

1. VA Worn of Women® contains a natural latex sponge at the closed end and a triangular-shaped outer anchoring structure.
2. The Woman's Condom® is packaged into a small capsule that dissolves and releases the condom when inserted into the vagina.
3. Phoenurse FC® is a dumbbell-shaped polyurethane condom with an insertion tool.
4. The Cupid is a latex condom in which the closed end contains a polyurethane sponge that helps hold it in place and is supposed to increase male pleasure.
5. The Panty Condom is a reusable nylon panty with rolled up polyethylene sheath placed in the crotch, and the panty is left on during sex.
6. The Origami FC is made of silicone and unfolds like an accordion when the penis pushed it into the vagina and is designed to be washed and reused several times. Origami is also developing an internal condom specifically for anal intercourse [21].

Contraceptive Diaphragm

The contraceptive diaphragm used to be one of the only contraceptive methods available to women. Over time, and with the advent of a greater variety of and more effective contraceptives, the diaphragm has fallen out of interest and has lower availability than before. All but one diaphragm needs to be fitted by a clinician and generally must be directly provided to the patient. The now available "one size fits most" Caya® diaphragm may be obtained with a prescription in some local drug

stores, mail order pharmacies, or online. The traditional diaphragm is a contoured silicone device, which is filled with spermicide and placed into the vagina so that the spermicide is applied to and covers the cervix. The device rests behind the pubic symphysis.

For traditional diaphragms, each woman must be sized and sizing must be repeated when the woman has a >10% weight change. Sizing the diaphragm should also be delayed 6–8 weeks following a pregnancy of at least 14 weeks. The diaphragm comes in eight sizes, with diameters ranging from 50 to 95 mm. The device should be comfortable, and the patient should not feel pressure when the device is in place.

The Caya® SILCS diaphragm is a single-size reusable diaphragm made of silicon that is designed to fit women who would normally wear size 65–80 mm diaphragms. The contoured shape was designed to better fit the female anatomy, with a thin cervical cup and pliable rim. The device allows for easy placement and removal as it has grip dimples that give the woman a tactile cue for where to hold and squeeze the rim and a removal dome under which a woman's finger can fit to remove the diaphragm. The device also contains a center point, which allows for appropriate positioning within the vagina. The Caya® diaphragm is currently available with prescription [22]. Some providers prefer that a potential user should have a "test fit," but otherwise the device does not require sizing. At that visit, the clinician can also verify that the woman can successfully place and remove the device.

Efficacy

The failure rate of the diaphragm is quoted to range from 6% to 12% for perfect use and from 12% to 18% for typical use [23].

Mechanism of Action

The contraceptive diaphragm acts as a physical barrier in the cervix, keeping semen from entering. In addition, spermicide is used with the diaphragm, thereby providing additional spermicidal activity.

Advantages

- Reusable
- May be combined with a male condom
- May be placed in advance of anticipated intercourse

Disadvantages

- Relatively high failure rate in many populations
- Requires fitting by a clinician
- Increases risk of recurrent cystitis and yeast infections [24]
- Risk of toxic shock syndrome (rare)

Patient Counseling/Instructions for Use

- The diaphragm must be used with every act of coitus.
- The dome of the diaphragm must be filled with spermicide prior to placement.
- To place the diaphragm, the woman may squat with one leg slightly elevated on a step. The diaphragm is then folded in half, and lubricant applied to leading edge. The diaphragm is then inserted into the vagina and guided upward and posteriorly within the vagina. The device should be allowed to open. The patient should check to make sure the diaphragm is covering the cervix and should tuck the upper edge of its rim behind the pubic bone.
- The woman must ensure that the diaphragm is in the correct position within the vagina prior to initiation of intercourse.
- The diaphragm should be left in place for at least 6 hours following intercourse and should remain in place for no longer than 24 hours.
- If another sexual encounter occurs again within 6 hours of a previous encounter, additional spermicide should be applied distal to the diaphragm, and the diaphragm should not be removed.
- If sex occurs again *after* 6 hours, the diaphragm should be removed, cleaned, and reinserted after additional spermicide is applied into the diaphragm and vagina.
- To remove the device, the woman places on finger in the vagina and slips it between the rim and vagina. Then, she should loop her finger around the rim and pull down and out of the vagina. The Caya® diaphragm has small grip dimples that help the woman find where to hold and squeeze the rim, as well as a removal dome under which the woman places her finger to remove the device.
- The diaphragm is contraindicated in those at high risk of HIV [1], as nonoxynol-9 spermicide can cause irritation and possible disruption of cervical mucosa leading to increased risk of infection and increased risk of viral shedding.

Cervical Cap

Femcap® is the only cervical cap currently available in the United States. A cervical cap is a soft silicone cup shaped like a sailor's hat that is placed deep into the vagina covering the cervix. The larger portion of the brim flares outward to push

Table 9.3 Cervical cap sizing

Obstetrical history	Cap size needed
Never been pregnant	22 mm diameter
Has been pregnant, never had vaginal delivery	26 mm diameter
Vaginal delivery	30 mm diameter

against the posterior vaginal wall to allow a snug fit into the fornices. The cap contains a loop for easier removal, though this loop has not necessarily been shown to be helpful [25]. The brim is longer posteriorly to fit the posterior wall of the vagina. Sizing of the cervical cap is based on the woman's obstetrical history (Table 9.3).

Efficacy

In a small randomized trial comparing the Femcap® to the All-Flex® diaphragm, the calculated typical use failure rate for Femcap® was 13.5% versus 7.9% for the diaphragm [26]. The manufacturer quotes a failure rate of 7.6 per 100 women per year, based on the second-generation Femcap® [27].

Mechanism of Action

The cervical cap acts as a barrier by covering the cervix to prevent sperm from entering the female upper genital tract, and the addition of N9 provides spermicidal activity.

Advantages

- May be placed 15 minutes to 40 hours prior to intercourse.
- Reusable.
- Can be used for multiple acts of intercourse for up to 2 hours without additional spermicide and can be left in place for up to a total of 48 hours.
- Can combine with the external condom to increase effectiveness.
- The cervical cap is made from silicone, which is very durable and cannot be punctured by fingernails, and lasts at least 2 years.
- Non-odorous and easy to clean.
- Can be used with any type of lubricant.

Disadvantages

- If sex had not been anticipated, sex must be interrupted to place the cap.

Patient Counseling/Instructions for Use

- The woman should place about one-fourth teaspoon of 2% nonoxynol-9 spermicide into the dome of the cap, which is the part that will cover the cervix. She should place another one-half teaspoon of the spermicide within the groove of the cap between the brim and dome, which faces the vagina when in place. Then, she should apply a thin layer of spermicide over the outer brim except where it is being held by the finger and thumb.
- The woman should choose a position for insertion – squatting, standing with one leg raised on a step, and reclining on back with both knees bent. The cap is then inserted, ensuring that the bowl is facing up and the longer brim is facing the body. The cap should be pressed inward and upward in the vagina and released over the cervix. The woman should ensure that the cap is covering her cervix completely.
- The FemCap® must be left in place for at least 6 hours following the last act of intercourse.
- To remove the cap, the woman should squat and bear down to bring the strap closer to her fingers. She should then press against the dome and rotate slightly to release suction. Then, she should grasp the loop and gently pull the cap down and out of the vagina. After use, the cap should be cleaned with antibacterial hand soap and rinsed with clean water.
- The CDC Medical Eligibility Criteria for Contraceptive Use indicates that the cervical cap should not be used in women with cervical intraepithelial neoplasia or cervical cancer, nor should it be used in women with distorted cervix anatomy [1].
- The cervical cap is considered MEC Category 2 for parous women due to its higher failure rate compared to nulliparous women [1].
- The cervical cap is contraindicated in those at high risk of HIV [1], as nonoxynol-9 spermicide can cause irritation and possible disruption of cervical mucosa leading to increased risk of infection and increased risk of viral shedding.

Contraceptive Sponge

The contraceptive sponge is a soft, polyurethane cushion measuring 2.5 cm in thickness and 5.5 cm in diameter with a dimple on the surface that covers the cervix, as well as a cloth loop on the opposite to allow removal. The contraceptive sponge

provides a physical barrier with spermicide, without the need for fitting or reapplication of spermicide as is necessary when using a diaphragm.

The Today® sponge was introduced in the United States in 1983 but left the market in 1994. It was again reintroduced in 2005 but became unavailable in 2007 when the manufacturer went bankrupt but returned to the market again in 2009.

The sponge is impregnated with 1 g of nonoxynol-9 spermicide. The woman adds liquid to the sponge to begin the release of spermicide. The sponge is placed in the vagina and covers the cervix. No additional spermicide is necessary for multiple acts of intercourse. The sponge must be left in place for at least 6 hours after intercourse, and one sponge cannot be used for long than 24 hours.

Because nonoxynol-9 may increase the risk of HIV transmission due to irritation and breaks in the cervical mucosa, this method should not be used for those at high risk of contracting HIV.

Efficacy

A Cochrane Review found the sponge to be less effective at preventing pregnancy than the diaphragm. A US study found a 12-month cumulative pregnancy rate of 17.4 per 100 women and 12.8 per 100 women for the sponge and diaphragm, respectively [28]. The failure rate quoted by Trussell [4] differs based on a woman's obstetrical history with higher failure rates in parous women for both typical use (24% vs. 12%) and perfect use (20% vs. 9%).

Mechanism of Action

The contraceptive sponge works in three ways to provide contraception: acting as a barrier to block the sperm from reaching the cervix, absorbing sperm, and releasing nonoxynol-9 spermicide to kill sperm.

Advantages

- Available over the counter
- Single use and disposable
- One size, does not require fitting
- Overall easy to place and remove
- Can be left in place for 24 hours for multiple acts of intercourse without need for additional replenishing of spermicide

Disadvantages

- Relatively high failure rate compared to other barrier methods
- Limited availability and expensive
- May cause allergic-type reaction including irritation and itching
- Increases risk of recurrent UTIs and yeast infection

Spermicide

Vaginal spermicides are substances which destroy sperm to prevent entry into the female upper genital tract. The only spermicide available in the United States is nonoxynol-9 which is a detergent that disrupts the plasma membrane and immobilizes sperm. Spermicide comes in a variety of forms, including foams, suppositories, films, and gels (Table 9.4).

Efficacy

When used alone for contraception, vaginal spermicides have failure rates that are much higher than several other contraceptive options [29]. Failure rates are quoted as 28% for typical use and 18% for perfect use [23]. Despite the relatively higher failure rates, the use of vaginal spermicides is more effective than no contraceptive use at all.

Table 9.4 Vaginal spermicides available in the United States

Type of spermicide	How to use	Time to activation	Duration of activity
Foam	Using applicator, release foam deep into vagina near cervix	Immediate	1 hour
Suppository	Advance high into vagina digitally	Wait 10–15 minutes to melt	1 hour
Film (VCF®)	Fold with fingers and advance high into vagina near cervix	Wait 10–15 minutes to melt	3 hours
Gels	Usually used with diaphragms and cervical caps	Immediate	1 hour alone; with diaphragm or cap, effective for one coital act

Mechanism of Action

The currently available spermicide in the United States, nonoxynol-9, is a detergent that disrupts the plasma membrane, causing sperm to become immobile.

Advantages

- Available over the counter
- No systemic side effects
- Many different forms to provide options for couples

Disadvantages

- Highest failure rates
- Can cause vaginal irritation
- Should not be used in couples with high risk of HIV transmission due to possible disruption of mucosa leading to increased transmission
- Can be messy

Future Developments

Several different compounds have been studied and are replacing nonoxynol-9 because they are less likely to disrupt the vaginal and cervical mucosa, thereby causing less irritation and avoiding the increased risk of transmitting and contracting sexually transmitted infections including HIV. BufferGel® is a nondetergent spermicide that maintains the slight acidity of the human vagina, thereby providing a protective mechanism [30]. An additional development is sodium cellulose sulfate, which is a noncytotoxic compound that inhibits sperm function [31]. More recently, Amphora®, a noncytotoxic, acid-buffering vaginal spermicide completed phase III clinical trials. Because of its microbicidal activity in addition to spermicidal properties, Amphora ® may also provide protection against sexually transmitted infections [32]. Amphora® may be used as a single agent, while BufferGel® is meant to be used with another barrier method, such as the diaphragm or cervical cap.

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Chapter 10
Emergency Contraception

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Introduction

Approximately 45% of all pregnancies in the United States are unintended [1]. Emergency contraception (EC) offers a "last chance" to prevent an unintended pregnancy. It should be made available to women who have had unprotected or inadequately protected sexual intercourse and who do not desire pregnancy. Currently in the United States, there are four major EC options available: progestin-only levonorgestrel (LNG) EC pills, combination oral contraceptives (COCs), a selective progesterone receptor modulator (SPRM) EC pill [ulipristal acetate], and the insertion of a copper T intrauterine device (IUD).

The most commonly used oral EC regimen is the single progestin-only pill.

The previously available two-pill progestin-only regimen instructed women to take one 0.75 mg LNG pill as soon as possible up to 72 hours after unprotected intercourse and to take the second 0.75 mg pill 12 hours after the first dose. However, research studies indicated that a single dose of 1.5 mg LNG was as effective as the two-pill regimen taken 12 hours apart and this led to the development of the 1.5 mg LNG single tablet product. Two-dose LNG-only EC pills are no longer sold in the United States. However, women who may have access only to the two-pill progestin-only pills should be instructed to take both pills together. There is evidence that progestin-only EC pills have some, although limited, effectiveness when initiated between 72 and 120 hours [2] after unprotected intercourse.

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The SPRM pill, ulipristal acetate, is FDA-approved for up to 120 hours after unprotected intercourse and is associated with a lower pregnancy rate during the 72 and 120 hour time window compared to progestin-only EC pills [3].

If women present for EC during this time frame, ulipristal acetate is preferred but its availability may be limited. In the United States, it is available by prescription only.

Combined estrogen–progestin oral contraceptives can be used as EC and the regimen used can be formulated from a variety of oral contraceptives, as listed in Table 10.1.

Table 10.1 Hormonal options for emergency contraception

Brand	Content	Pills per dose
Progestin-only EC pills: Take one dose within 72 h after unprotected intercourse		
Plan B one-step (FCH), next choice one dose (Actavis), my way (Gavis), take action, Afterpill (syzygy)	1.5 mg LNG	1
Progesterone receptor modulator pill: Take one pill within 120 h after unprotected intercourse		
Ella (Actavis)	30 mg ulipristal acetate	1
Combined (estrogen and progestin) oral contraceptives: Take two doses 12 h apart		
Cryselle® (Teva), Elinest (Novast), low-Ogestrel® (Actavis)	30 μg EE plus 0.3 mg NOR	4 + 4
Altavera (Sandoz), Amethia (Actavis), Camrese (Teva), Chateal (Afaxys), Introvale (Sandoz), Jolessa (Teva), Kurvelo (Lupin), Levora (Actavis), Marlissa (Glenmark), Nordette (Teva), Portia (Teva), Quasense (Actavis), Seasonale (Teva), Seasonique (Teva), Setlakin (Novast)	30 μg EE plus 0.15 mg LNG	4 + 4
Ayuna (Aurobindo), Enpresse (Teva), Levonest (Novast), Myzilra (Novast), Triphasil (Wyeth), Trivora (Actavis), Vienva (Sandoz)	30 mg EE plus 0.125 mg LNG	4 + 4
Afirmelle (Aurobino), Amethia Lo (Actavis), Aubra (Afaxys), Aviane (Teva), CamreseLo (Teva), Falmina (Novast), Lessina (Teva), LoSeasonique (Teva), Lutera (Actavis), Orsythia (vintage), Sronyx (Actavis)	20 μg EE plus 0.1 mg LNG	5 + 5
Amethyst (Actavis)	20 μg EE plus 0.09 mg LNG	6 + 6

EC emergency contraceptive, *LNG* levonorgestrel, *EE* ethinyl estradiol, *NOR* norgestrel

The most effective EC is the copper T IUD, which can be inserted within 5 days of unprotected intercourse. The use of the levonogestrel-containing IUD as EC is currently being investigated.

The availability of over-the-counter products specifically packaged, labeled, and marketed as emergency contraception has resulted in an increase in use over time. The proportion of women 15–44 who have ever had intercourse who ever used ECPs increased from 2% in 2002 to 18% in 2011–2013 [4].

Mechanism of Action

The primary mechanism of action of SPRM EC pills [ulipristal acetate], combined estrogen plus progestin EC pills, and progestin-only EC pills is inhibition or delay of ovulation [5–8].

Other proposed mechanism of action of the hormonal EC pills includes thickening of cervical mucus, alterations in tubal transport of sperm or ova, impairment of corpus luteum function, and inhibition of fertilization. There may also be endometrial changes that prevent a fertilized egg from implantation [7]. However, no clinical data exist that support these other mechanisms of action.

EC pills do not cause abortion or harm an established pregnancy [5, 9].

When being used as a routine method of contraception, the copper IUD primarily prevents fertilization by affecting sperm transport and function [10, 11]. It is likely that use of the copper IUD for emergency contraception includes this action along with a variety of other antifertility effects, including disruption of the endometrium and prevention of implantation.

Effectiveness

Regardless of the time period a woman has unprotected sex, the sooner EC pills are taken the more effective they are [12]. If LNG-only EC pills are used properly within 72 hours of unprotected intercourse, the risk of pregnancy falls to 1%.

The effectiveness of the method is measured by comparing the number of pregnancies expected in a sexually active population with the number of pregnancies actually occurring in that population following treatment. The expected pregnancy rates are highly dependent on the specific day of the menstrual cycle that each woman in the population had unprotected sex and a host of other factors affecting fecundity [13].

- The estrogen–progestin EC regimens prevent approximately 47–53% of expected pregnancies [13, 15].
- If levonorgestrel-only pills are specifically taken, the risk of pregnancy is reported to be reduced by 52% and 100% [14].
- For LNG and SPRM EC pills, the risk of pregnancy may be increased in obese women when compared to nonobese women.
  - The risk of pregnancy is higher in LNG EC pill users with a body mass index (BMI) of 26 or higher and PRM users with a BMI of 35 or higher [14].
- The effectiveness of the SPRM pill ranges from 62% to 85% [13].
- Insertion of a copper-releasing IUD reduces the risk of pregnancy by up to 99% [16].

Advantages

Advantages of EC Pills

- EC pills are safe for most women.
- No serious side effects associated with EC pills.
- Progestin-only EC pills are available over-the-counter without prescription or age restrictions.
- Progestin-only EC pills can be used by women who are not candidates for combination OCs.
- EC pills can be bought or provided in advance for use in an emergency.
- In the event of a failure, no teratogenicity or other adverse outcomes are reported after exposure to EC pills [17].

Advantages of Using a Copper IUD for EC

- The copper IUD is the most effective EC method.
- The copper IUD can provide an ongoing highly effective method of contraception.
- The copper IUD can be inserted up to 5 days after unprotected sex.

Disadvantages

- Combination EC pills are associated with a high rate of nausea (42%) and vomiting (16%) [18] and pretreatment with an antiemetic is recommended.

- Not all women know about EC options or know how to get access to them.
- Many women do not know that they can use some types of birth control pills as EC.
- There is only a 72–120 hours window (depending on method) in which to start the first dose.
- There is no protection from sexually transmitted infections (STIs) or HIV. Opponents link emergency contraception to abortion or that it may encourage sexual activity among teenagers. Research studies report that increased availability of EC pills does not result in increased unprotected sexual activity [19, 20]. In some states where prescriptions are necessary, "conscience laws" allow pharmacists to refuse to fill prescriptions for EC pills.
- There is confusion between EC pills and the abortion pill RU-486 (mifepristone).
  - RU-486 is *not* an EC pill. It is taken *after* pregnancy is established (within 49 days of the last menstrual period).

Indications

Indications for EC include the following conditions:

- Unplanned, unprotected act of sexual intercourse
  - Condom breakage or improper use
  - Diaphragm, cap, or shield slippage
  - Missed OCs (especially missing the first week of OCs)
  - Late in starting a new patch or vaginal ring
  - Late in getting depot medroxyprogesterone acetate (DMPA) or depo-subQ provera 104™ injection
  - Mistake in calculating "safe days" when practicing fertility awareness methods
- Sexual assault [21]

Side Effects

No deaths or serious side effects have been linked to emergency contraception use.

Common side effects of LNG EC regimen are nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), change in menstrual bleeding (26%), dizziness (11%), breast complaints (11%), other complaints (10%), vomiting (6%), and diarrhea (5%) [22]. SPRM and LNG EC have similar adverse effect profiles. LNG-only EC pills have a lower rate of adverse events than the estrogen–progestin (Yuzpe) EC pill regimens:

- Nausea: 23% [2] in Plan B compared with 50% on estrogen–progestin EC pills
- Vomiting: 6% in Plan B compared with 19% on estrogen–progestin EC pills

Effect on Menses

After EC pills, most women will start their next menses within 1 week before or after the expected time [22]. After taking LNG EC, some women may have spotting for a few days. At the time of the expected menses, about 75% of users have vaginal bleeding similar to their normal menses, 13% have heavier bleeding, and 12% bleed less. The onset of this next menses is within 7 days of the expected date in 87% of users, whereas 13% experience a delay of more than 7 days. If there is a delay in the onset of the next menses of more than 1 week, pregnancy should be considered.

> Generally, regular bleeding occurs within the week or month after EC pill use and resolves spontaneously.

Ectopic Pregnancy

> There is no evidence that pregnancy that occurs after EC pill use will more likely be an ectopic one [23].

Contraindications

There are a very limited number of medical contraindications to treatment with EC pills:

- Women who are pregnant (EC pills cannot terminate an established pregnancy).
- Undiagnosed vaginal bleeding.
- Allergy to any component in medication.
- Not intended for geriatric (age 65 and older) or pediatric populations.
- Not recommended for routine use as a contraceptive.

Progestin-only and SPRM EC pills are preferable to combination EC pills for women with the following conditions:

- History of thromboembolic disease.
- Vascular disease.
- Heart disease.
- Focal migraines.

- Liver disease.
- Some health care providers prefer to use progestin-only ECs in patients for whom combination OCs are contraindicated; however, because of the short duration of treatment, this is not routinely necessary.

Eligibility requirements for the copper IUD are the same as for insertion for routine use as listed in Chap. 9. Of particular importance, however, is ruling out the presence of active cervicitis and performing risk-based screening for STIs.

Fetal Effects

There is no evidence that exposure to EC pills will harm a fetus. Studies in women who have accidentally taken OCs containing levonorgestrel during early pregnancy report no adverse effect on the fetus.

Counseling Tips

The progestin-only and SPRM EC pills are more effective and have fewer side effects than the estrogen–progestin EC pills and are thus the preferred method.

- No clinician exam or pregnancy testing is necessary before providing or prescribing EC pills.
- The most common side effects related to EC pill use are nausea, vomiting, menstrual irregularities, breast tenderness, headache, abdominal pain and cramps, and dizziness.
  - Another dose of EC pills should be taken if a user vomits within 3 hours of ingestion. Use of an antiemetic should be considered [24].
- It is very important to counsel the woman that use of ECs is not 100% effective.
- EC pills may be less effective in women with higher BMIs; this may be seen more in LNG users than SPRM EC pill users.
- Following treatment, users should be counseled to get a pregnancy test and seek medical care if her period does not start within 3 weeks.
- Counsel regarding regular use of a contraceptive method after EC use.
  - OCs, POPs, vaginal ring, DMPA, or patch can be started immediately the day after EC pill treatment is completed, or alternatively started with onset of next menses (use barrier methods while waiting).
  - Insert IUD or contraceptive implant during the next menstrual period; consider using a copper IUD for EC treatment.
- Consider risk-based screening for STIs.

- A follow-up physical or pelvic exam is needed if there is concern about either the general health of the user or the pregnancy status after treatment.
- Although there is limited data, a rapid return to normal ovulation and fertility is typical.

Options

Product Prepackaged as Dedicated EC Pills

- Ella (ulipristal acetate 30 mg) is indicated for up to 120 hours after unprotected intercourse.
- Plan B One-Step and its generic products contain one 1.5 mg levonorgestrel tablet to be taken within 72 hours of unprotected sex.
- Progestin-only pills are still moderately effective up to 120 hours after unprotected intercourse and can be made available to patients who request it up to 120 hours after intercourse.

Combination OCs Containing Levonorgestrel or Norgestrel

The FDA issued a summary statement in the *Federal Register* in 1997. This statement is reassuring to clinicians using OCs for this off-label indication.

The FDA is announcing that the Commissioner of Food and Drugs has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception.

- Combination OCs containing either levonorgestrel or norgestrel are used in specific regimens based on the Yuzpe method (Table 10.1).
  - The first dose of two to six pills is taken as soon as possible within 72 hours of unprotected intercourse and the second dose is taken 12 hours later.
  - Pretreatment with an antiemetic is recommended.

Copper IUD (ParaGard®)

Insertion of the copper IUD is the most effective EC method when inserted within 5 days of unprotected intercourse and can provide ongoing highly effective contraception for up to 12 years.

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Chapter 11
Female Tubal Sterilization

Traditional and Research Methods

Charles M. March

Introduction

In 2001, 3.1 million (48%) of the 6.4 million pregnancies that occurred in the United States were unintended [1]; 52% of these unintended pregnancies occurred in women who had not used contraception during the month in which they conceived. Between 2001 and 2008, the rate of unintended pregnancies increased slightly; however, between 2010 and 2014, the rate of unintended pregnancies fell to 44% [2]. In developed countries, the rate of unintended pregnancies fell by 30%, whereas in developing countries, the rate of unintended pregnancies fell only 16%. In 2011, 42% of all unintended pregnancies ended in abortion; by 2014, this number had decreased by 12%. Among those 15–44 years old, the rate of unintended pregnancies that ended in live birth decreased from 27/1,000 in 2008 to 22/1,000 in 2011. Between 2010 and 2014, 59% of unintended pregnancies in developed countries ended in abortion compared to 55% in developing regions.

> Although the first tubal sterilization was performed more than 140 years ago, it took many years before it gained widespread acceptance. Today, surgical sterilization is a simple, safe, and cost-effective method of achieving long-term contraception. It remains the second [behind oral contraceptives (OCs)] most widely used form of contraception in the United States.

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Using data from the National Survey of Family Growth, Daniels and Abma reported that between 2015 and 2017, 64.9% of all women in the US aged 15–49 were using a method of contraception [3]. For 18.6% of them, it was female sterilization, 12.6% chose an OC, and 8.7% relied upon condoms. The emergence of sterilization as a popular method of avoiding pregnancy paralleled the introduction of OCs. Both methods became readily acceptable at the time of the "sexual revolution." Data from the same source, but reporting on women aged 15–44, indicated that the use of sterilization was 15.5% between 2011 and 2013, 16.5% between 2006 and 2010, and 16.6% in 2012 [4].

As expected, the use of sterilization increases with increasing age: 4.2% for ages 20–29, 21.6% for ages 30–39, and 39.4% for those 40–49 years of age. Female sterilization is the most common method of contraception worldwide, used by 19% of all women of ages 15–49 years who are married or in a relationship [5]. Reliance on female sterilization is highest in Asia (23.4%), followed by Latin America and the Caribbean (26%) and lowest in Africa (1.7%) and Europe (3.8%). Higher rates of female sterilization are found in women with public insurance or no insurance, African American women and Hispanic women not born in the United States. and in women with self-reported cognitive disabilities compared to those with physical disabilities or with no disabilities [6].

Analyses of ethnic backgrounds and races reveal significant differences in the rates of surgical sterilization. In the United States, sterilization is more common among Native Americans (42%) compared to Black women (36%), White women (30%), and Asian women (17%) [7]. Reasons for undergoing surgical sterilization also vary greatly: prior surgical sterilization was considered as voluntary by more than 75% of Black women, almost 60% of White women, and almost 50% of Native Americans. In contrast, only 40% of Hispanics and 30% of Asians considered their prior sterilization to be voluntary. Sixty percent of Asians indicated that they felt pressure to undergo surgery.

Whether related to some of the data presented in the previous paragraph, or to concerns related to issues of regret, a 2017 Committee Opinion of The American College of Obstetricians and Gynecologists stresses the importance of discussing reversible methods of contraception, especially long-acting reversible contraception and when appropriate, vasectomy, at the time of counseling regarding sterilization [8–10].

The previous strict guidelines for performing sterilization that coupled age and parity were dramatically relaxed with the introduction of laparoscopy, making female sterilization an outpatient procedure. Laparoscopy is safer and cheaper than laparotomy, provides a superior cosmetic result, and allows a woman to resume normal activities sooner. The increased safety of anesthesia coupled with concerns about the long-term safety of OCs and intrauterine devices (IUDs) continues to drive interest in permanent sterilization. Features of the "ideal method" of sterilization are listed in Table 11.1.

Table 11.1 Attributes of the ideal method of sterilization

Minimal skill and training required
Performed by paramedical personnel
One-time procedure
Highly effective
Effective immediately
Office procedure
Local or no anesthesia
Minimally invasive
Minimal pain
Minimal morbidity
No mortality
High patient privacy
Little equipment required
Reusable equipment
Equipment maintenance minimal
No visible scar
Performed during pregnancy, postpartum or post-abortion
Inexpensive
Reduce/prevent STDs
Reversible

Popularity

The percentage of women who use sterilization as a method of contraception rises from about 5% in women between 20 and 24 years of age to almost 50% for those between 40 and 44 years of age. It is a safe (in both the long and short term), highly efficacious, cost-effective procedure that requires a single act of compliance, separates contraception from sexual activity, and does not rely on partner behavior.

> Sterilization's ability to achieve long-term contraception with a single event is unique and is an important reason for its popularity. This feature makes sterilization an ideal method of permanent contraception in developing countries where access to health-care providers is limited.

Although vasectomy is faster, safer, less complex, equally effective, and less costly than the methods available to women, more women than men undergo sterilizing procedures, the current ratio being approximately 3:2. Although many ill-founded concerns about the short- and long-term consequences of vasectomy have reduced the willingness of some men to undergo surgery, other important factors are likely to maintain the current ratio. Among the factors driving female sterilization procedures is the high rate of cesarean section that is driven by multiple factors, including an increasing number of older primiparas, as well as those with multiple

gestations, prior uterine surgery, convenience, and the current litigious environment. The ready access to the oviducts at the time of cesarean section makes simultaneous sterilization a convenient option. Postpartum sterilization via a small periumbilical incision is also a convenient option because recovery from both the delivery and the extra surgery can occur at the same time, obviating the need to return for an interval procedure. The desire to remain in control of one's reproductive health is another critical reason for the popularity of female sterilization. Whereas more than 95% of men who have undergone vasectomy are or were married, over 18% of sterilized women have never been married [11].

Health Benefits of Sterilization

The most widely touted and significant health benefit of tubal sterilization appears to be a reduced risk of ovarian cancer.

One large prospective study that followed 396,000 women for 9 years found that the risk of ovarian cancer was 30% less in the group who had undergone tubal ligation [12]. This finding has been confirmed by other investigators. Although the mechanism is unknown (perhaps tubal closure protects the ovary by preventing carcinogens from ascending into the upper reproductive tract), this is a most welcome benefit. The "anti-ovarian cancer" benefit of salpingectomy is discussed later.

Tubal closure does not prevent colonization of the lower female reproductive tract by sexually transmitted organisms, but it does reduce the risk of salpingitis and pelvic peritonitis.

Contraindications

Contraindications to sterilization are few. The primary absolute contraindication is patient ambivalence. Patients with reduced capacity are not candidates for sterilization. Those with gynecologic malignancies and those with associated pelvic pathology are better served by treatment directed at treating their primary disease.

Traditional Sterilzation Methods

Approaches to female sterilization are listed in Table 11.2. Factors which influence the decision of the approach to be used include timing, that is, the proximity to a pregnancy, the need for other gynecologic surgical procedures, specific health issues

Table 11.2 Methods of female sterilization

Associated with pregnancy
Postpartum (with cesarean section or minilaparotomy)
Pomeroy or modified Pomeroy partial salpingectomy
Parkland, Uchida, Irving, Madlener, fimbriectomy, total salpingectomy, hysterectomy
Post-abortal—Minilaparotomy or laparoscopic
Interval
Laparotomy
Parkland, Uchida, Irving, Madlener, fimbriectomy, total salpingectomy
Mini-laparotomy
Parkland, Uchida, Irving, Madlener, fimbriectomy, total salpingectomy
Laparoscopy
Fulguration, clips, rings, loops
Vaginal
Blind transcervical, chemicals, tissue adhesives
Hysteroscopic
Endometrial ablation?
Hysterectomy

such as cardiac or pulmonary disease, obesity, prior pelvic infections or prior abdominal or pelvic surgery. Other important factors include the training, experience, and skill of the surgeon (or non-medical health worker), the cost of using and maintaining the equipment, and the availability of general anesthesia. Sterilization may be performed in close proximity to a pregnancy or it may be an "interval" procedure. The techniques, along with the advantages and disadvantages of the different methods, are discussed in the subheadings below. Each of these methods should be evaluated against the backdrop of the "ideal method." The method of sterilization selected should be the one that the surgeon believes to be the most efficacious and the one with which he or she has the most experience and comfort. Performing a procedure that the surgeon has had little experience with is likely to have a lower success rate.

Postpartum Methods

Sterilization at the time of cesarean section or immediately following a vaginal delivery is popular, cost-effective, and convenient. A number of investigators have reported that only about one-half of those who had planned to undergo sterilization during the immediate postpartum period actually do [13–17]. Characteristics of those who did not undergo sterilization at that time include increased body mass index, being married, having had little or no prenatal care, initial request in the second trimester, having undergone a vaginal delivery, being African-American, having a medical problem, lack of time in the operating room and "change of mind." Of

those who did not follow through with plans at the time of delivery, 44% underwent laparoscopic tubal sterilization later and 18% became pregnant again [13].

There are additional risks to sterilization in the puerperium that deserve consideration. The postpartum pelvic viscera are more vascular and thus the risk of excessive bleeding is higher at this time. Generally, however, bleeding is usually recognized immediately and controlled easily and quickly. Bleeding is rarely of clinical significance and reoperation, the need for transfusion, and occurrence of anemia are very uncommon complications.

Most concerns are related to the issue of regret. Tubal sterilization at the time of cesarean section presents a unique situation because the desire for no more children often rests on the assumption that the newly delivered infant will be viable and healthy. Unfortunately, this outcome is not a certainty and a reevaluation of whether or not the procedure should be performed may be necessary in some circumstances. A difficult pregnancy and/or the delivery of an infant whose health status is uncertain or grave are causes for concern. Is the request for sterilization emanating from a reaction to a physically, emotionally, or financially difficult pregnancy? Would a neonatal or infant death cause the couple to desire another pregnancy?

Often, the delivery of a very ill infant is not anticipated, and the topic had not been discussed. In any case, delivery of a neonate with medical uncertainties or adverse outcome should prompt a reevaluation of the couple's wishes before performing the procedure. If the delivery is by elective cesarean section under regional anesthesia, a discussion with the mother is possible. After a vaginal delivery, the delay before minilaparotomy provides a time interval to allow a more thorough evaluation of the options. Avoidance and management of regret are covered more completely at the end of this chapter.

> Sterilizations should not be performed between eight and 41 days after delivery because of an increased risk of complications [18].

On occasion, patients in whom a cesarean section is planned (prior cesarean section, previous myomectomy by laparoscopy or laparotomy with one or more deep myometrial incisions) and those who have uterine pathology which would benefit from hysterectomy will be candidates for cesarean hysterectomy. Although this procedure has more morbidity than a cesarean section, it is of great value in carefully selected patients.

Partial Mid-Tubal Salpingectomy: Pomeroy, Modified Pomeroy, Parkland, Madlener, Uchida, and Irving

Although there are many methods of interrupting the oviducts at the time of cesarean section, some modification of the Pomeroy partial salpingectomy procedure is the most common. The modified Pomeroy procedure is also a popular method used during postpartum and interval minilaparotomies. The postpartum minilaparotomy

is performed through a small sub-umbilical incision because the enlarged uterus allows easy access to the fallopian tubes.

Regardless of the approach, all modified Pomeroy procedures begin with a positive identification of each fallopian tube by following its course laterally to locate the fimbria. The mid-portion of the fallopian tube is then elevated with a Babcock clamp and the approximately 2-cm knuckle of tube that is created, is ligated with no. 1 plain catgut suture. After the suture has been tied and cut, the ends are grasped with a small Kelly clamp and used to steady the tube. The 2-cm knuckle of tube, still elevated with the Babcock clamp, is cut, one side at a time, about 3–5 mm above the suture tie. Generally, a small section of mesosalpinx is also removed, and the specimen is sent to pathology to provide histological confirmation. The cut ends of the tube should not be too close to the ligatures because they may slip and cause delayed hemorrhage. The rapidly dissolving plain catgut suture allows the ends to separate early in the postoperative period.

Many variations of the procedure are performed, including the use of different absorbable sutures, coagulation of the ends of the tubes, and repeat ligation of the cut ends. All these procedures have similar success rates. In the Parkland modification, after a segment of the mid-tube is removed, both cut ends are religated. In the Madlener procedure, the tube is crushed and then tied with permanent suture. Because of its high failure rate and lack of a specimen for histological review, this procedure is rarely performed. The Uchida and Irving procedures were designed to reduce the risk of tuboperitoneal fistulae. Although advocates claim that they are slightly more effective, they take longer to perform and opponents insist that they have a slightly higher morbidity. The use of clips or bands is not recommended in the postpartum patient because the tubes are dilated and more vascular, making the devices difficult to apply, resulting in a high failure rate.

Fimbriectomy and Salpingectomy

Tubal sterilization is often now done by salpingectomy due to a potential reduction in ovarian cancer. On occasion, when significant tubal pathology is discovered, sterilization is best accomplished by salpingectomy. Benefits of salpingectomy are discussed below. It is important that all clamps and sutures be placed as close as possible to the fallopian tube so that the mesosalpinx and collateral blood supply to the ovary is spared during excision.

Kroener fimbriectomy was developed as a single-suture alternative to salpingectomy that would have a low risk of recanalization and failure. Unfortunately, this procedure does not appear to be more effective and it has four important disadvantages. The first is that the procedure often leaves a substantial proximal segment ending with a small section of ampulla where fluid may collect and form hydrosalpinges. These can become quite large and may cause pain, undergo torsion, become infected, or may be interpreted as neoplasms. Any of these complications can lead to surgical intervention. Secondly, unless the fimbria-ovarica is incorporated in the suture, a tuboperitoneal fistula and subsequent pregnancy, often ectopic, may occur.

Thirdly, the intrauterine pregnancy rate after reversal of a bilateral fimbriectomy is significantly lower than that following mid-tubal sterilization [19]. Finally, hydrosalpinges have an adverse effect upon the success rate of in vitro fertilization should the patient elect such treatment in the future [20].

Post-abortal Methods

Following a spontaneous abortion or elective pregnancy termination, sterilization may be performed by any of the methods described above for the postpartum patient as well as those described in the section below devoted to laparoscopic methods. The same admonition applies for these patients as for those who are postpartum, that is, to be certain that the request for sterilization is not primarily a reaction to the circumstances surrounding the pregnancy.

Interval Methods

Sterilization at a time removed from pregnancy (at least 6 weeks after a term delivery or a few weeks following an abortion) is the most common in the United States. When requesting an interval sterilization, the patient is able to make the decision without the stress of pregnancy or any related complications, and with the knowledge of the health status of all her children. Interval procedures are most safely performed in the follicular phase of the menstrual cycle because at that time it is very unlikely that the patient is pregnant and it avoids bleeding from trauma to a recent corpus luteum.

Laparotomy

The same operations performed at the time of cesarean section (as discussed above) can be performed via interval laparotomy. Rings or clips may also be applied but are more often used during a laparoscopic procedure and are discussed below. Except for certain patients who have contraindications to laparoscopy (morbid obesity, multiple prior abdominal or pelvic laparotomies, and severe cardiac or pulmonary disease), laparotomy is rarely performed for the sole indication of sterilization unless in conjunction with a laparotomy mandated by other pelvic or abdominal pathology not amenable to laparoscopic treatment. Addition of the tubal ligation procedure adds little cost or morbidity and affords the patient significant benefits. Educating general surgeons to inquire about a patient's desires for future childbearing during the counseling session for non-emergent gallbladder or intestinal surgery is a valuable milestone.

Minilaparotomy

Minilaparotomy employs a small (2–3 cm) suprapubic incision and is performed under local, regional, or general anesthesia. Except for very obese patients, access to the fallopian tubes is generally easy. This procedure is performed in the lithotomy position and a uterine elevator is employed to facilitate access to, and identification of, the oviducts. The introduction of a paracervical block before application of the uterine manipulator reduces significantly the discomfort for those who elect local anesthesia. Tubal occlusion may be obtained by a partial or total salpingectomy or by a variety of implants (bands or clips) that are discussed in the "Laparoscopic Approach" section. Minilaparotomy is often performed on an outpatient or overnight basis. If significant pelvic pathology is present, the incision may have to be enlarged and regional or general anesthesia used.

Vaginal Approach

Tubal sterilization may be performed via a colpotomy incision. The procedure is usually performed in the follicular phase on an outpatient basis, and the problem of cul-de-sac infection has been virtually eliminated by the use of preoperative prophylactic antibiotics. After entering the peritoneal cavity through a colpotomy incision, fimbriectomy or partial salpingectomy is the most common technique. If the latter is employed, tubal ligation is often accomplished using an Endoloop, although Filshie or Hulka clips or Falope rings can also be used with ease and success [21]. Another vaginal approach is entry via culdoscopy, a procedure that had been employed to investigate infertility prior to the advent of laparoscopy. This technique has been abandoned.

Sterilization via colpotomy is performed infrequently despite the advantages of the vaginal approach. Perhaps the main reason for its fall in popularity is the overall reduction in the amount of vaginal surgery performed for prolapse or urinary incontinence. As average parity has fallen and the frequency of cesarean section has risen, prolapse of pelvic organs is less common. Surgery to treat urinary incontinence is commonly treated by a suprapubic rather than a vaginal approach. Thus, recent graduates of residency programs have less experience in performing vaginal surgery. Even in the absence of clinical infection, adhesions of the oviducts and/or ovaries to the site of incision or vaginal scarring at that site may occur, resulting in dyspareunia.

Laparoscopic Approach

Although the first laparoscopic sterilization was performed in 1936 by Bosch in Switzerland, the reintroduction of laparoscopy in the late 1960s had a most dramatic impact on interval sterilization. At that time, the prime indications for laparoscopy were diagnostic (to investigate the cause of pelvic pain or infertility). Laparoscopy

offered a faster, safer and cheaper method of sterilization than laparotomy or mini-laparotomy with a shorter recovery period and a superior cosmetic result.

Before beginning surgery, all equipment should be checked to verify that all is in proper working order. Either closed or open laparoscopy is an acceptable approach, and both can accomplish the goal of safe placement of the primary trocar. Thus, the choice is driven primarily by operator preference. In closed laparoscopy, a Veress needle is introduced blindly into the peritoneal cavity followed by the insufflation of carbon dioxide, or direct primary trocar placement followed by insufflation. The latter permits more rapid insufflation, but if a vital structure is injured, the size of the wound is larger. After the primary trocar has been placed, a laparoscope is introduced and the pelvis visualized.

In open laparoscopy, a small (but larger than for closed laparoscopy) subumbilical incision is made and the peritoneum is entered under direct vision. A primary trocar is then placed and anchored to the fascia with sutures or secured in place by an inflatable base. It is important to obtain an airtight seal to prevent the soon-to-be-insufflated carbon dioxide from leaking from the peritoneal cavity. The benefit of open laparoscopy is that the peritoneum is entered under visualization, not blindly, thus making it a good approach for those with prior abdominal or pelvic surgery and/or known or suspected adhesive disease. Although the data demonstrate that the frequency of inadvertent damage to structures is identical between open and closed procedures, these data may be biased because more high-risk patients may have been selected for open laparoscopy. Another option for patients who are likely to have adhesions in the periumbilical region is closed laparoscopic entry into the left upper quadrant.

Disposable closed laparoscopic trocars have a spring-loaded cover that retracts when meeting significant resistance, allowing the blade to be exposed during entry. After the peritoneum is entered and there is no further resistance, the blade retracts and is covered. This was designed as an added degree of safety and therefore is the choice.

A hybrid approach, blending open and closed laparoscopy techniques, is to introduce the Veress needle and then to enter the peritoneum with an optical trocar after the carbon dioxide has been introduced. This type of non-bladed optical trocar has a somewhat sharp and transparent tip. The telescope is passed into the trocar and with gentle pressure, the preperitoneal layers are dissected under direct visualization until the peritoneum is reached, and a “window” is identified through which the trocar and telescope are advanced. In short, this is another attempt to reduce the risk of major visceral or vascular injury.

The laparoscope may be of the operating type that has an accessory channel that can be used as a port for introduction of an operating instrument, or a diagnostic laparoscope with only the telescope. The latter requires the placement of a secondary trocar for the introduction of the operating instrument. Although the use of an operating laparoscope permits the operation to be performed more rapidly and uses only one incision, its primary advantage is that (in carefully selected patients) it allows sterilization to be performed under local anesthesia. The goal is rapid identification and occlusion of the oviducts when a thorough pelvic inspection is not

needed. For an obese woman, local anesthesia, minimal peritoneal distention, and minimal Trendelenburg positioning may not permit good visualization and safe surgery. For these patients, those with pelvic adhesions, or those with symptoms such as pelvic pain, the alternative choice is the use of a diagnostic laparoscope with a secondary trocar, which permits complete inspection of the pelvis as well as appropriate surgical intervention.

A "microlaparoscope" (2.0–3.0 mm in diameter) may also be used to perform sterilizations under local anesthesia in an office setting using bipolar tubal coagulation [22]. Advantages include a significant reduction in cost and postoperative pain as well as an increase in privacy. Future improvements in technology may make this approach a more viable one.

Laparoscopic Electrocoagulation Methods

The original method of tubal sterilization was via monopolar coagulation. In this procedure, the mid-portion of the oviduct is grasped with an electrode and elevated away from all other pelvic structures before coagulation. As electrocoagulation proceeds, the area of destruction of the tube becomes white. The desired "endpoint" of the procedure is propagation of the area of destruction of the fallopian tube of approximately 1.5 cm in both directions from the site of electrode placement. Usually a small portion of mesosalpinx immediately below the site of application of the forceps is also coagulated. Commonly, the tube is cut and divided in the center of the burned area. Both cut ends may or may not be recoagulated. This method is rapid and highly effective.

Three potential problems are associated with this method. The first is the formation of tuboperitoneal fistulae and subsequent failures, many of which are ectopic pregnancies. Initially, this occurrence was considered surprising, especially because the white area of injury does not typically extend to the cornual portion of the uterus. To solve this problem, it is recommended that tubal coagulation be performed in the isthmic-ampullary junction, well away from the uterotubal junction. Overall, the frequency of ectopic pregnancies is not high, but the proportion tends to rise as the interval from the time of surgery increases [23–25]. This fact suggests that failures occurring early in the postoperative period may be related to technique, whereas failures which occur subsequently are likely related to self-repair of the oviducts. The greater spread of damage during the application of monopolar injury does have two important advantages: superior hemostasis and a very low failure rate. Even if the placement of the monopolar electrode is not perfect, the diffusion of the burn tends to compensate.

The second problem is that there is often only a small amount of fallopian tube remaining, making sterilization reversal difficult or impossible: the residual fallopian tubes may be represented solely by small cornual stumps and a few tufts of fimbria. Clearly, greater-than-expected tubal damage occurs during monopolar coagulation. Siegler et al. demonstrated that lateral spread of monopolar energy is

much greater than that judged at the time of application and characterized a "burst" effect of monopolar energy [26].

The third problem of monopolar tubal sterilization is the occurrence of delayed bowel injuries, estimated to occur in between 1/360 and 1/7,300 procedures [27]. This complication has led to legal action and battles over whether these injuries resulted from an unrecognized "sparking" from the electrode to the bowel or from surgical error with direct touching of the large and/or small bowel by the electrode. Soderstrom reported that, based on the histologic appearance of the site of injury, most injuries were related to trauma from the Veress needle or a trocar rather than an electrical injury [28].

If the surgeon detects what is judged to be a very small serosal burn, he or she has a dilemma. Such injuries are likely to heal without incident [29]. Although these data suggest that the patient may be observed, it may be difficult to ascertain with certainty that the injury is not a deeper one, and many surgeons will oversew the area of injury. However, if the area of the burn is larger or if injury beyond the serosal layer is suspected, bowel resection including a 5-cm margin on each side should be performed. Attempts to oversew such an area will usually fail because of the significant occult damage that occurs with the use of unipolar electrodes. In the postoperative period, the area of burn and suture placement may undergo necrosis and bowel perforation and peritonitis may ensue. Hybrid trocars, that permit some of the electrical charge to be transferred and stored in the telescope or in another instrument, are no longer used because it was demonstrated that injuries could come from "capacitive coupling" when these instruments were used [30].

These three problems led to a drop in the popularity of monopolar tubal sterilization and by 1980, bipolar forceps had replaced unipolar electrodes in most centers [31]. Because the electrical energy is transmitted only between the two jaws (electrodes) of the forceps, several of the problems related to monopolar electrode use were solved immediately: neither capacitive coupling nor "sparking" can occur, and the lateral spread of the energy is reduced greatly. Truly, "what you see is what you get" and provided the electrodes are placed 2 cm or more from the uterotubal junction, fistulae will almost never occur. Women sterilized by bipolar tubal coagulation prior to age 30 had the highest probability of having an ectopic compared to those who had a postpartum partial salpingectomy (31.9 vs 1.2 ectopic pregnancies per 1,000 procedures) [25]. Lowest rates of ectopic pregnancy were reported among those who had either unipolar coagulation or a postpartum partial salpingectomy.

Because the extent of the tubal damage is not extensive, reversal of sterilization is usually possible if only one area is coagulated. In an effort to minimize the risk of failure when using bipolar forceps, double- and triple-burn techniques are employed commonly. Even a double-burn approach does not eliminate failure. Gunston et al. analyzed the gross and microscopic appearance of the fallopian tubes of 35 patients who underwent sterilization via a double-burn bipolar approach and who subsequently conceived and later underwent bilateral salpingectomy [32]. Although all had appeared to have occluded tubes based upon macroscopic appearance, only 22

had bilateral tubal occlusion when their tubes were examined microscopically. Some have challenged reports indicating that the failure rate of bipolar sterilization is higher if only a single area is coagulated, and claim that a single burn is adequate as long as it is done properly. Because blanching and swelling of the portions of the oviduct within and adjacent to the electrodes do not ensure that the innermost portion of the tube has been desiccated, it is advisable to use a generator with an ammeter. This device provides both visible and audible signals to the surgeon indicating when the area has been properly and thoroughly coagulated.

Although the double-burn and triple-burn approaches reduce the failure rate, the "promise" of possible reversal is mostly eliminated. The frequency of bowel injuries has fallen with the use of bipolar electrodes, but whether this is related to inherent equipment differences, an overall improvement in surgical equipment, or the increased experience of surgeons remains unclear. If a single-burn bipolar technique is used, many surgeons divide the tube in the center of the coagulated area. The area of coagulation and the incision should include only a minimal amount of mesosalpinx, because further damage may compromise ovarian blood supply, lead to excessive bleeding necessitating further coagulation, or rarely, cause delayed hemorrhage and reoperation. If the oviduct is divided, coagulating the proximal and distal stumps again reduces the risk of both fistula formation and postoperative bleeding. A 5-mm tripolar device which combines a bipolar electrode with a cutting blade is also available. This device eliminates the need to exchange an electrode for scissors and reduces operating time slightly.

Another choice, the endocoagulator, was designed to reduce the risk of damaging internal structures such as bowel and ureter [33]. With an endocoagulator, heat (as opposed to electrical energy) is applied directly to the tubes. By avoiding the conversion of electrical energy to heat in the tubes, this procedure may offer added safety. Few surgeons, however, use an endocoagulator for any other laparoscopic or open procedure and thus its availability is limited. This instrument has not gained widespread use for sterilization.

Laparoscopic Mechanical Methods

Tubal occlusion by mechanical means avoids the concerns of safety associated with electrosurgery but generally is not used in situations in which tubes are dilated, such as in the immediate postpartum period. There are three common devices and each has its own idiosyncrasies. Each device is highly effective, has a unique applicator and a different mechanism of achieving tubal occlusion. Because each device is somewhat unique, it is advisable that each surgeon identifies his or her preferred method. Whether that decision is based on ease of use, perceived efficacy, cost, or other factors, the surgeon should ideally use the chosen method exclusively and use an electrosurgical method as backup. Efficacy of a procedure is greatest when the nuances of each instrument are learned through prolonged experience.

Laparoscopic Silastic Rings (Yoon Band/Falope Ring)

The 3.6-mm silastic band is mounted on a 6-mm applicator that is inserted into the pelvis through an accessory trocar [34]. This band is impregnated with 5% barium sulfate which provides radio-opacity. Only *immediately* before application to the oviduct, the band is stretched and advanced over the outer cylinder of the applicator. If the band remains on the applicator in a stretched condition for an extended time period, it may lose "memory" and thus some occluding capacity. The fallopian tube is grasped at the junction of its proximal and middle thirds and elevated. An approximately 2.5 cm portion of tube is drawn into the inner cylinder of the applicator. The surgeon must ensure that the tube is encircled completely (not simply a tangential application) by the jaws of the instrument so the band will seal the tube completely. Next, the ring is advanced from the outer cylinder over the tubal segment. It is important to confirm that the ring is "seated" properly over the knuckle of tube. Improper placement may allow tubal motility to cause the ring to slide off the tube. Proper application of the jaws to the oviduct must be accurate to avoid incorporating any mesosalpingeal vessels. The placement process should be slow, deliberate, and controlled, ensuring that minimal tension is placed on the oviduct and that no tearing of the oviduct or mesosalpinx occurs. Tearing of either of these structures may lead to early or delayed hemorrhage. Usually, the segment of tube within the band is not excised. The Falope Ring system is available as either a single-use disposable kit or a reusable applicator.

Intraoperative application of a local anesthetic to the site of ring application can alleviate some of the postoperative pain associated with this procedure. If one or both oviducts are large, if bleeding occurs, or if adhesions are present, conversion to an electrosurgical method of tubal sterilization is advised. Failure rates are approximately 1% after 2 years. Over time, the bands become peritonealized. In most cases, the lack of an excessive inflammatory reaction, minimal adhesion formation, and the small amount of tube damage make this method of sterilization highly reversible. As mentioned above, these bands can be placed via the vaginal approach.

Laparoscopic Clips

The Hulka spring-loaded clip has two Lexan plastic jaws with multiple teeth [35]. The lower jaw has a distal hook. The jaws are joined with a stainless steel hinge pin. After the isthmic portion of the oviduct is identified, the jaws are placed over this tubal segment perpendicular to its long axis. This right angle application of the clip is mandatory and may necessitate double-puncture laparoscopy. After proper placement, the jaws of the clip are closed and a gold-plated stainless steel spring is advanced over the jaws, sealing the tube. The teeth of the clip must extend into the mesosalpinx, ensuring complete closure of the tube. Because the amount of damage to the tube is minimal (3 mm), this method of sterilization is very amenable to

reversal. However, as is true for all tubal sterilization procedures, those that induce the least amount of damage are associated with the highest failure rate over time, again testimony to the regenerative powers of the fallopian tubes [36].

The Filshie clip uses a specially designed applicator that can be used with a diagnostic or operating laparoscope or during laparotomy [37]. The titanium clip is lined with silicone rubber and has a concavity on its antimesenteric side which conforms to the shape of the oviduct. Application of the clip must be perpendicular to the tubal isthmus and is facilitated by using a secondary trocar. Initially, the clip occludes the tube by the pressure applied during application. However, as tubal necrosis ensues, the silicone rubber expands and maintains luminal obstruction. Only 4–5 mm of tube is damaged, facilitating reversal of sterilization. Both types of clips can be placed via the colpotomy approach.

Laparoscopic Salpingectomy

Salpingectomy, whether by laparoscopy or laparotomy, has an important role among sterilizing procedures. Patients with hydrosalpinges should not undergo mid-tubal interruption because it is likely that the isolated segment(s) will become large, cause pain, and may be mistaken for a neoplasm. After extensive adhesiolysis, a severely damaged tube may have little, if any, normal-appearing portions and removal may be advised. If laparoscopic sterilization is done in conjunction with endometrial ablation, the small isthmic segment of oviduct may fill up with blood or secretory products from the uterine horns, and cause the "post-ablation, post-tubal sterilization syndrome" [38]. Some of these patients have undergone hysterectomy. However, combining both procedures does not increase the risk of subsequent hysterectomy [39].

Removal of the lateral intramural segment during salpingectomy or leaving the lateral troughs of the endometrial cavity intact during the ablation may reduce the risk of the post-ablation tubal sterilization syndrome [40].

If salpingectomy is performed, the incision should be placed immediately below the oviduct to spare the collateral ovarian blood supply. At least in the short term, salpingectomy does not appear to have an adverse effect upon ovarian reserve as measured by changes in serum levels of follicle-stimulating hormone (FSH) and anti-Mullerian hormone (AMH) [41, 42].

Qin et al. reported that the total dose of FSH needed during IVF cycles, the numbers of oocytes recovered, and the clinical pregnancy rate were the same in those post salpingectomy patients compared to control groups [43]. Their data contradict those of other investigators [44, 45]. Although a reduction in ovarian blood supply and basal antral follicle count has been reported on the side of salpingectomy compared to the contralateral side, that difference may be related to the pathology that was the indication for the salpingectomy rather than the procedure itself [46, 47]. In the study by Qin et al., the investigators reported

that levels of AMH and early follicular phase levels of FSH were higher in those who had undergone salpingectomy, thereby raising concern about long-term reduction in ovarian reserve [43].

These reports are important because interest in salpingectomy as the preferred method of sterilization has increased recently secondary to data linking the development of ovarian cancer to intraepithelial carcinomas in the fallopian tube [48–54]. These data caused Kaiser Permanente Northern California to issue a policy statement in 2013 recommending salpingectomies for surgical tubal sterilization and at the time of hysterectomy [55]. During the study period (June 2011–May 2016), 10,741 tubal sterilization procedures were performed. In the final year of the study, salpingectomy accounted for 78% of interval laparoscopic sterilization procedures and 9% of intra- and postpartum procedures. Operating times were increased minimally as was blood loss in the patients who underwent a cesarean section and those who had a postpartum procedure.

In a cost-effective analysis, it was suggested that in a population of 10,000 women undergoing salpingectomy at the time of cesarean section, there would be 17 fewer diagnoses of ovarian cancer and 13 fewer deaths [56].

Laparoscopic Complications

Both morbidity and mortality of laparoscopic procedures remain low. A 1993 American Association of Gynecologic Laparoscopists' report indicated a death rate of 1 in 22,966 procedures. In another report, the US mortality rate was 1.5 per 100,000 procedures with many of the mortalities occurring in patients with preexisting medical conditions [57]. Although a significant number of deaths may be attributed to anesthetic complications, vascular and intestinal injuries also account for some of the mortality. Patient selection, intraoperative and postoperative vigilance, and operator experience and judgment influence the rate of serious complications and the success rate of the surgical procedure.

Overall, the rates of minor and major complications are approximately twice as high among women who undergo a minilaparotomy with a partial salpingectomy compared with those who have laparoscopic tubal coagulation. However, the types of complications tend to be different. With minilaparotomy, longer operating times, longer convalescence, higher rate of wound infections, and greater postoperative pain predominate, whereas vascular and bowel injuries, although rare, are the significant complications of laparoscopic procedures. However, surgeon and patient selection are important factors in determining which procedure was selected.

In a literature review, Llarena et al. reported that bowel injuries occurred in between 0.01% and 0.03% of laparoscopic sterilization procedures [58]. Careful inspection of the pelvis immediately after entry and again before removing the instruments is necessary to reduce the frequency of a delay in diagnosis. Delays can be associated with severe morbidity, multiple repeat operations, and even death. A death rate of 1 in 31 was reported if the diagnosis of bowel injury was delayed [58].

A little-discussed "complication" is the inability to complete the procedure laparoscopically with the necessity to convert to a laparotomy. Rather than a true complication, these events are usually owing to technical issues related to adhesions, poor visualization, or difficult port placement.

However, the possibility of inability to complete the procedure laparoscopically should be mentioned during the preoperative discussion.

The low frequency of complications coupled with the low risk of method failure makes sterilization one of the safest and most effective methods of preventing pregnancy. It is obviously the ideal choice for those in a stable, long-term relationship who are certain that they do not wish to conceive in the future. Methods that reduce the amount of tubal damage are preferable because they are less likely to interfere with ovarian blood supply and less likely to cause adhesion formation. Procedures that minimize tubal damage also facilitate reversal should circumstances change in the future.

Sterilization does not affect the functioning of the ovaries or other endocrine organs, alter the age of menopause, change sexual function or desire, or increase the risk of hysterectomy [59, 60]. Psychological problems and sexual dysfunction do not occur more often following sterilization. Although irregular menses and dysmenorrhea have been reported to occur more often after tubal sterilization, most of these reports include a large number of women who had used oral contraceptives for painful menses and/or cycle regulation prior to the surgery [61–64]. *A review of CREST data by Peterson* et al. *did not demonstrate that menstrual abnormalities are more common after sterilization* [65].

Laparoscopic Failures

Failures can be either early or late: the former are usually related to technique (incomplete tubal occlusion or application of clip, ring, or electrode to a structure other than the tube) and the latter related to tubal recanalization or formation of a tuboperitoneal fistula. Failures are more common in younger women, probably because there is more time for tubal recanalization and a greater likelihood that they will have a high proportion of quality oocytes if recanalization occurs. For all of the procedures performed by laparoscopy, failure rates of around 1–2% are reported.

Failure rates vary according to the method used (Table 11.3), but generally are between 0.1 and 0.8% during the first year [66].

Table 11.3 Cumulative 10-year failure rates of tubal sterilization by abdominal approach

Method	*Failure rate (%)*
Postpartum partial salpingectomy	0.75
Unipolar coagulation	0.75
Silastic ring	1.77
Interval partial salpingectomy	2.01
Bipolar coagulation	2.48
Hulka clip	3.65
Filshie clip	2.5

In the US Collaborative Review of Sterilization (CREST) study, 10,685 women were enrolled. The 10-year cumulative probability of pregnancy was 18.5 per 1,000 procedures. However, for postpartum and laparoscopic procedures using unipolar tubal coagulation, the rate was 7.5 pregnancies per 1,000 compared with 36.5 per 1,000 after Hulka-Clemens clip application. For bipolar tubal coagulation, the rate of failure was reduced if three or more sites were coagulated [67]. In the CREST study, luteal phase pregnancies, estimated to occur in 2 or 3 per 1,000 procedures, were not reported as failures. Curettage at the time of sterilization does not completely insure that a procedure will not "fail" because of a preexisting pregnancy [68]. A more prudent approach is limiting surgery to the follicular phase of the cycle that will also reduce the risk of traumatizing a fresh corpus luteum.

The greater the time that has elapsed between the surgery and the younger the age of the patient at the time of surgery, the higher the cumulative pregnancy rate will be [69]. These authors concluded that failures within the first year after surgery were more likely to be intrauterine and secondary to non-occlusion of the tube(s), whereas pregnancies which occurred more than 1 year postoperatively were more likely secondary to tubal regeneration and more likely to be ectopic.

In a review of 140 failures after sterilization, Date *et al.* reported that 57 % of these occurred after minilaparotomy, 38 % after a laparoscopic procedure, and 4 % after cesarean section [70]. It was estimated that most conceptions occurred secondary to a tuboperitoneal fistula. Additionally, improper surgical technique was judged to be the cause of failure in 19 % of the failures and spontaneous recanalization in 18 %. Fourteen of the pregnancies were extrauterine. The likelihood that a pregnancy will be extrauterine is greater if it occurs after a sterilizing operation. The longer the interval between sterilization and the occurrence of a pregnancy, the greater the likelihood that it will be extrauterine: the proportion of ectopic pregnancies increases over time, being three times higher 4–10 years after surgery than in the first 3 years. If a pregnancy occurs after tubal sterilization, ectopics are most common after bipolar coagulation (65%) and interval partial salpingectomy (43%). In a randomized trial involving 13,209 women, unipolar coagulation (17%) and spring clip application (15%) were reported to be associated with the lowest proportion of ectopic pregnancies [71].

Transcervical Approach

Transcervical sterilization has a host of advantages (Table 11.4) and has been the goal of many dedicated to finding the ideal method of population control. The lack of an incision is an important advantage because it affords a quicker recovery.

Table 11.4 Advantages of transcervical sterilization

Office procedure
Greater patient privacy
Less invasive
Local/no anesthesia
No incision
Safe
Effective
Inexpensive
Rapid recovery
Ideal for high-risk patient

The shorter operating time and diminished postoperative pain are attractive advantages of this approach as is the lower initial lower cost which is maintained during the first 6 months after surgery [72–74]. Performance in an office increases patient privacy. The ready access to the tubal ostia and the proximal portions of the fallopian tubes makes this method most attractive. It has long been hoped that a simple transcervical sterilization technique be developed that could be easily performed by paramedical personnel. Ensuring that the endometrium in the periosteal areas is thin improves visibility greatly and reduces the risk of failures. Choices include timing the surgery for the early follicular phase and/or endometrial suppression prior to surgery. The use of a long-acting endometrial or pituitary suppressant provides both a thin endometrium AND postoperative contraception while waiting for a hysterosalpingogram to provide evidence of bilateral tubal closure [75].

However, the intramural oviduct has unique properties that, to date, have proven impossible for all transcervical approaches to overcome.

The intramural oviduct is quite tortuous, often having convolutions in excess of 360° in a length of less than 2 cm, thereby preventing the introduction of long, rigid devices [76]. The uterine muscle enveloping the proximal portion of the tube undergoes contractions that can dislodge intraluminal plugs. The tube is somewhat compliant and it may dilate after a device is placed, thus preventing complete microscopic occlusion, which is essential to prevent sperm transport. Tubal secretory capability is known to prevent the adherence and tissue in-growth needed for some devices to be effective. Finally, as is true with the more distal oviduct, healing and regeneration may lead to failures.

Transcervical sterilization has a number of important disadvantages (Table 11.5). An important disadvantage is that transcervical sterilization must be performed in the early proliferative phase of the cycle at a time well removed from a pregnancy. Even more important, however, is that none of the methods in use today are effective immediately.

Contraindications specific to hysteroscopic sterilization include known abnormalities of the uterus or fallopian tubes, which would hinder visualization or tubal

Table 11.5 Disadvantages of transcervical sterilization

Complex delivery systems
Expensive disposables
Long learning curve
Follicular phase timing required
Normal anatomy required
Not possible postpartum
Not possible post-abortion
Possible intraperitoneal injury
Delayed efficacy
Long-term effectiveness unknown
Long-term risks uncertain
Insurance coverage variable

cannulation, current or recent pelvic infection, allergy to contrast media, pregnancy or suspected pregnancy, and delivery or pregnancy termination within the past six weeks.

Essure® Micro-Insert

In April 2018, the FDA issued an order to restrict the sale and distribution of the Essure device because of available research data outlining the risks associated with placement of this device including migration, fragmentation, and tubal perforation. In December 2018, the FDA extended Bayer's mandatory follow-up of women enrolled in the study from 3 years to 5 years. On December 31, 2018, Bayer stopped selling and distributing Essure in the United States.

The Essure micro-insert, approved by the U.S. Food and Drug Administration in 2002, gained widespread acceptance. The insert is a 4-cm-long device consisting of a flexible, stainless steel inner coil, a very elastic expandable outer coil of a nickel titanium alloy (Nitinol), and a layer of polyethylene terephthalate running along and through the inner coil.

The insert is introduced into the intramural portion of the oviduct under hysteroscopic guidance. An operating hysteroscope with a 5F instrument channel is used. Surgery is performed under local anesthesia in the proliferative phase. Using a narrow-diameter release catheter, the device is maintained in a "wound-down" configuration (0.8 mm in diameter) to facilitate placement. After the tubal ostium has been identified, the insert is advanced into it until only 5–10 mm remains visible. The device is disengaged from the release catheter and the outer coil expands to up to 2 mm, anchoring the device in place and spanning the distance between the intramural and proximal isthmic portions of the tube. The polyethylene terephthalate fibers induce a foreign body reaction that peaks 2–3 weeks after placement of the coil. Over the next 3 months, tissue in-growth occurs, completely occluding the tube and anchoring the device in place permanently. This in-growth begins at the

periphery of the device and enters its interior. Overall, approximately 5 cm of tube is affected. The reaction spares the uterine and tubal serosa as well as the tubal epithelium distal to the device [77]. Another method of contraception is used until a hysterosalpingogram (HSG) demonstrates bilateral tubal obstruction [78]. However, more patients were likely to comply with recommendations for follow-up by ultrasound (88%) vs those who were advised to have an HSG (77.5%) [79]. Unfortunately, both HSGs and other imaging studies have not always been interpreted accurately and "late" migration, that is, after HSG confirmation of proper placement had been documented 6 months after surgery [80–82].

Successful placement can be achieved in more than 84–98% of women at the time of initial attempt [83]. Obstacles to successful placement include severe cervical stenosis, poor visualization of tubal ostia due to endometrial proliferation (too late in menstrual cycle), lesions obstructing tubal ostia, markedly eccentrically located ostia, and marked obesity [84]. The safety, efficacy, and patient satisfaction were demonstrated in prospective, multicenter trials involving more than 700 patients [85]. Adverse events were reported in 7% of patients. Almost all who had successful placement reported being happy with the method. Proper device placement and bilateral tubal occlusion were demonstrated in 96% of women 3 months after surgery. Almost all others had occlusion documented after another 3 months. Similar high rates of success and low rates of complications were reported in a study from Italy which involved 1968 women [86]. Contrary to "conventional wisdom," it was reported that the successful placement rate of the Essure device was similar when surgery was performed by 39 experienced hysteroscopic surgeons (98%) or by 37 "novice" physicians (96.1%) [87]. Patient characteristics such as BMI, past surgical history parity, and number of prior vaginal deliveries were similar, and mean operating times were less than three minutes longer when performed by novices.

After placement of the insert by experienced hysteroscopists, 87% relied on the method for permanent contraception. After 9,620 women-months of exposure to intercourse, no pregnancies were reported [88]. Of the 643 women followed up for 5 years, there were no pregnancies in 29,357 women-months of follow-up [89]. In a 2015 publication which reviewed the data from 13 centers of 449 patients who relied on Essure inserts for 5 years after HSG evidence of bilateral tubal occlusion and satisfactory device location, no pregnancies were reported [90]. In another study of 1,200 women, only three pregnancies occurred after 7,200 months of surveillance and all occurred in the first year of follow-up [91]. In a review of 24 pregnancies, 10 were judged to be secondary to perforation, seven to expulsion, and seven to unilateral placement (only two of these patients had undergone a salpingectomy on the contralateral side), and almost all were considered secondary to physician or patient non-compliance [92]. However, almost one-third of the pregnancies were secondary to misinterpretation of the test used to confirm bilateral tubal obstruction.

Three important cost benefits accrued to those who underwent Essure rather than laparoscopic sterilization: reduced procedural costs (mostly because of the anesthesia and facility charges associated with laparoscopy are obviated), less time away

from work and reduced needed for ancillary assistance (baby sitting or other) [93]. Compared to laparoscopic sterilization, hysteroscopic procedures are associated with a higher initial failure rate and a higher rate of reoperation at 1 year [94, 95]. However, the latter group of investigators also reported that those in the hysteroscopic sterilization group were older, had a greater likelihood of having a prior history of pelvic inflammatory disease, major abdominal surgery, or cesarean section, and were more than ten times likely to undergo reoperation [96]. Although these inserts have been placed in more than 750,000 patients, almost always successfully, and although the rate of adverse events within the first 30 days of insertion has been reported to be 0.2%, recent reports have documented thousands of late failures associated with migration of the inserts, fragmentation, and perforation at the uterotubal junction [97, 98].

Overall, the frequency of long-term adverse effects including pelvic pain, abnormal bleeding, perforation of the fallopian tube(s), has been reported to be between 1.1% and 4.3% [99, 100]. Perforation of the fallopian tube, fragmentation of the device, and migration into the mesentery of the small and large bowel have been reported [101]. Those with complaints of pelvic pain and/or abnormal bleeding after Essure placement had a higher frequency of these complaints prior to sterilization compared to those without these complaints preoperatively [102–104].

Hysterectomy was also more frequent in those with preexisting complaints. These statistics are similar to those in the post laparoscopic patients. Among patients who underwent removal of their implants via a laparoscopic or hysteroscopic approach, up to 40% reported complete resolution of symptoms, but up to one-third reported unchanged or worsening symptoms [105, 106]. Of those whose pelvic pain was a "new symptom" after Essure placement, 50% had complete resolution within 3 months after removal [107].

Adiana Permanent Contraception System

The Adiana device accomplishes sterilization using a two-step procedure that has been evaluated in the EASE (**E**valuation of the **A**diana System for Transcervical **S**terilization Using **E**lectrothermal Energy) trial that was completed in mid-2005. Although the protocol had many similarities to the Essure trials, this device and its method of achieving sterility are considerably different. The Adiana System received FDA approval in 2009, but was withdrawn from the market in 2012 because of poor sales and claims of patent infringement in disputes with the manufacturer of the Essure Micro Insert.

Under hysteroscopic guidance and in the proliferative phase of the menstrual cycle, a catheter is placed into the intramural portion of the tube. An electrode at the

distal end of this catheter delivers a low level (<5 W) of radiofrequency energy, causing superficial destruction of the epithelial layer. The radiofrequency generator output is automatically regulated to maintain a desired tissue temperature during lesion formation. This approach limits the amount of damage induced but also individualizes treatment to compensate for variations in patient anatomy including distal tubal obstruction, tubal spasm, and convoluted intramural fallopian tube anatomy [108]. Exact placement of the catheter in the center of intramural portion with 360° contact is critical to the induction of a symmetrical circumferential injury. After the lesion is created, a porous non-biodegradable matrix implant of medical-grade silicone is deposited in the area. The process of tubal repair induces tissue in-growth into the matrix and complete tubal occlusion. Proper placement is documented visually and by ultrasound in the immediate postoperative period. An HSG and follow-up ultrasound are performed 3 months after surgery. Reports of postoperative pain were markedly less compared to the frequency of that complaint in those treated with Essure. The cumulative failure rates were 1.08% at 1 year and 1.82% at 2 years [109]. Although these effectiveness rates are within the range of all sterilization methods evaluated by the CREST study at similar time intervals, they are high for all methods evaluated in the study, except for spring clip application [110]. The three-year cumulative ectopic pregnancy rate was 3.7/1,000 [111].

Because of the above-detailed problems with mechanical devices placed hysteroscopically, new animal research has focused upon a biodegradable implant of nanoparticles of iron oxide which are heated [112]. Both biocompatibility and fibrotic healing were demonstrated in a feline uterine horn. Further research may lead to human studies. These same investigators have examined the introduction of a previously frozen tubal insert of collagen in acetic acid slurry into rat horns which had been de-epithelialized immediately prior to insertion [113]. Fibroblast infiltration was detected within 6 days and occlusion of the horn was demonstrated at 30 days.

Research Transvaginal Techniques

AltaSeal

AltaSeal is a medical-grade stainless steel implant (similar to a coronary stent), which provides mechanical closure of the fallopian tubes rather than relying on tissue in-growth around the implant to provide occlusion. After insertion of the device into the intramural portion of the fallopian tube, two barb-tipped wings are deployed within the fallopian tube and anchor it in place. In an initial feasibility study of ten patients with benign disease, an attempt was made to place this device hysteroscopically immediately prior to hysterectomy [114]. Because of distortion by fibroids, placement and assessment of tubal patency were possible in only 9 of 20 tubes. Closure was verified in eight (89%). In a subsequent study of efficacy, 22 patients had the device implanted and were followed up for 1,150 women-months (all for at least 3 years and some as long as 4 years). To date, neither adverse

effects nor pregnancies have been reported [115]. Because of patient discomfort during the procedure, the device was modified so that the distance between the barbs was reduced from 4.5mm to 3 mm and the overall length of the implant was reduced from 16 mm to 12 mm. Similar promising results were reported in a study from the Netherlands [116]. Of the 19 women with unilateral or bilateral hydrosalpinges, 18 had successful placement of the AltaSeal device prior to undergoing in vitro fertilization. Tubal obstruction was proven by HSG 1 day and again 12 weeks after hysteroscopy; 8/18 women conceived (26% of IVF attempts) and 7 delivered.

ReLARC

A "blend" between reversible long-acting reproductive control and hysteroscopic surgery is the ReLARC device, which was developed as a reversible alternative to hysteroscopic sterilization [117]. Two types of devices are available: one which releases copper and another which releases levonorgestrel. Both are fixed to a size 0 monofilament polypropylene suture. The suture has a knot at its end which allows it to be anchored within the myometrium at the top of the fundus in the midline under hysteroscopic guidance. Advantages include the following: easier placement in the midline rather than having to access eccentrically placed tubal ostia if treatment is to be standard hysteroscopic sterilization; documentation of there being no intrauterine pathology prior to application of the device; size smaller than that of an IUD and therefore a lower risk of expulsion; and fewer complaints of pain and/or excessive uterine bleeding. At follow-up visits, proper placement can be verified by ultrasound.

Alternative Uses

In what should be considered "role reversal," both the Essure and the Adiana devices have been utilized in patients with infertility secondary to distal tubal disease and the presence of a hydrosalpinx on one or both sides [118, 119]. Following oocyte retrieval and fertilization, the success rate of embryo transfer in patients with this type of tubal pathology is reduced, but increased after salpingectomy or other methods of isolating the toxic hydrosalpingeal fluid from the pre-transfer uterine environment [120, 121]. In a literature review comparing the placement of Essure to other interventions prior to embryo transfer, the authors found both a higher pregnancy rate compared to no intervention (36% vs. 13%). However, they also reported a higher miscarriage rate (38%) compared to those who had no intervention (30%) vs 16% after salpingectomy or tubal aspiration, 15% after other methods of tubal occlusion, and 2% after tubal division prior to embryo transfer [122].

Hysteroscopic Failures

Failures of hysteroscopic sterilization can be divided into two categories: those whose postprocedural HSG demonstrated bilateral tubal occlusion and those patients who did not undergo that study as well those who conceived prior to the required three-month interval between surgery and HSG. Cleary et al. analyzed 20 reports following Essure placement which they judged to be of "fair quality" and found no reports of pregnancies in 11 studies in which postoperative documentation of bilateral tubal obstruction had been documented [123]. These patients had been followed up for between 7 months and 7 years. In contrast, 102 pregnancies were reported in the 11 other studies. All but 15 of these pregnancies occurred either prior to the three-month "waiting" period or in those who did not have documentation of bilateral tubal obstruction. Using a Markov model, Gariepy and associates developed expected pregnancy rates per 1,000 women at one and 10 years after sterilization by hysteroscopy to be 57 and 96, respectively, or after silicone band application by laparoscopy (seven and 24) or after bipolar coagulation (three and 30) [124]. Other investigators have reported that the failure rates after laparoscopic or hysteroscopic procedures were similar [125, 126]. Brandi et al. reported 997 pregnancies among 817 women who had undergone either laparoscopic (610 pregnancies in 42,391 women) or hysteroscopic sterilization (387 pregnancies in 27,724 women) [127]. Those who conceived after hysteroscopic sterilization had fewer extrauterine pregnancies and were more likely to have live births.

Endometrial Ablation

Any tubal sterilization procedure can be combined with one of the global methods of endometrial ablation in women who desire sterilization and treatment for menorrhagia. Irrespective of the method of endometrial ablation used, it cannot be considered a method of sterilization. Although the number of reported pregnancies after endometrial ablation is quite low, perhaps 1 in 400, these data are difficult to interpret. Many women who undergo ablation are older and thus relatively infertile. Many others have had sterilizing operations or use contraception. In some of the pregnancies that have occurred after endometrial ablation, there have been serious complications. Simultaneous hysteroscopic sterilization adds little operating time to the ablation, avoids the risk of post-ablation tubal sterilization syndrome, and is an ideal combination for the high-risk patient.

In a record review of 5,484 women who underwent endometrial ablation between ages 30 and 39 and who were followed up for a period of 39,892 women years, three were diagnosed with endometrial cancer [128]. The common symptom of possible endometrial cancer, abnormal bleeding, will be absent in patients who have undergone an endometrial ablation and became amenorrheic. Thus, these patients should have a pelvic ultrasound examination at the time of their periodic gynecologic examination in order to detect any

silent and excessive endometrial proliferation. These investigators also reported that the risk of hysterectomy was increased fourfold in the post-ablation group compared to matched controls. Risk factors for hysterectomy in the post-ablation group included the presence of leiomyomas, younger age, prior cesarean section, as well as tubal sterilization.

Hysterectomy

Hysterectomy for sterilization is associated with a longer recovery period, more morbidity and mortality, and is more costly than tubal sterilization. Costs included are those related to surgery, anesthesia, medications, and hospitalization, as well as those related to lost time from work and childcare. Nevertheless, when associated conditions exist, hysterectomy may be considered. Associated conditions include menorrhagia, leiomyomata, pelvic relaxation, severe cervical dysplasia, endometriosis, and significant dysmenorrhea. If possible, hysterectomy should be vaginal because of the lower morbidity and faster recovery time. If the patient has significant pain mandating inspection of the pelvis and/or significant pelvic adhesions, laparoscopically assisted vaginal hysterectomy is appropriate.

Avoiding and Managing Regret

In a study of 7000 women followed up for at least 5 years after sterilization, the frequency of regret increased over time and was reported to be 6% overall [129]. The frequency of regret within 14 years after surgery was 20.3% for women who were under 30 years at the time of surgery, and 5.9% in those above that age.

Those under 30 indicated regret because of the desire to have more children, whereas those over 30 attributed gynecological or medical disorders to the sterilizing procedure, a claim not supported by data. There were three age-related demographic factors present in those who requested reversal of sterilization: younger age at sterilization, younger age at first delivery, and younger age at last delivery [130]. With respect to age at the time of sterilization, a literature review indicated that those who were below 30 years of age at the time of sterilization were twice as likely to express regret, between 3.5 and 18 times more likely to request information about reversal, and eight times more likely to undergo either reversal or an evaluation for in vitro fertilization [131]. As might be expected, those who were divorced and remarried were more likely to request reversal. Finally, the salaries of those requesting reversal were significantly lower. Other important factors include

ambivalence about future childbearing, negative attitudes toward sterilization, dominance of the decision-making by the woman's husband, and conflict with her husband during the decision-making process [132]. The death of an infant or a child is also an important factor [133].

Additionally, the frequency of regret varies by ethnic background and race: 60% of Native American women, 41% of Hispanic women, 33% of Asian women, 32% of White women, and 26% of Black women who had been sterilized want more children later in life [134]. Parous women and women in unstable relationships are more likely to regret having undergone sterilization than are nulliparous women. In some studies, regret is reported to be more common among those who had a postpartum sterilization [135]. Among postpartum patients, regret is more common among those who had been delivered by cesarean section compared to those who had a vaginal delivery [135]. The probability of regret decreases as the time from the last birth increases. After 8 years, it falls to approximately 5%, not different from the rate of regret among all women.

Obviously, careful counseling by an experienced health-care professional is critical to reducing the frequency of regret [136]. The physician is involved in this process, especially when the method of sterilization is discussed. Those candidates for sterilization requesting a "reversible" method are obviously going down the wrong path. Many factors to consider are discussed in a 2017 Committee Opinion from the American College of Obstetricians and Gynecologists [137].

Reversal of Sterilization

Henshaw and Singh reported that 26% of couples who had a tubal ligation or vasectomy desired more children [134]. One study reported that 14.3% of women requested information about the possibility of a reversal over a fourteen-year period [138]. Overall, 2% of patients will request reversal [138]. Factors affecting the success of reversing tubal sterilization are listed in Table 11.6. Unlike vasectomy, the success rate of reversal does not appear to be related to the number of years during which the tube(s) was(were) occluded (when corrected for age and the presence of other infertility factors) [133].

The amount of damage induced by surgical sterilization (in decreasing order) is multiple-burn monopolar coagulation, Uchida or Irving procedures, fimbriectomy, multiple-burn bipolar coagulation (with or without tubal division), single-burn bipolar coagulation, partial salpingectomy, and Falope Rings and clips [139]. *Obviously, the less the extent of tubal damage, the higher will be the overall pregnancy rate after tubal reconstruction and the lower will be the rate of ectopic pregnancy* [140].

Table 11.6 Factors that influence the success of tubal sterilization reversal

Method of sterilization
Amount of tubal damage
Patient's age
Presence of other infertility factors
Surgeon's experience

The chance of successful surgical reversal is inversely related to the amount of damage. Data assessing the likelihood of reversing hysteroscopic sterilization are not as plentiful but are encouraging [141]. Monteith et al. performed 95 bilateral tubouterine implantations in patients who wished to conceive after prior hysteroscopic sterilization procedures [142]. Of the 70 patients who were followed up for at least 12 months, 25 patients conceived 31 times. Eight pregnancies ended in spontaneous abortions. Of 25 patients who had shorter periods of follow-up, there were seven pregnancies: five were ongoing, and there was one abortion and one ectopic gestation that was treated with methotrexate.

After a physician receives a request for a reversal of sterilization, a referral should be made to a reproductive surgeon experienced in tubal microsurgery. A review of the prior surgery and pathology reports, if available, and an HSG aid in determining the amount of remaining proximal and distal tubal length and help to predict the chance of successful reanastomosis. If the HSG shows intrauterine pathology, hysteroscopic correction of the defect(s) would be added to the surgery. If the intrauterine disease is significant, correction should be attempted prior to reversing the tubal sterilization because uncorrectable uterine pathology would mandate consideration of a gestational carrier.

After these data are gathered, an informed discussion of the two alternatives [in vitro fertilization (IVF) and reconstructive surgery] for restoring fertility follows. The couple may base their decision on multiple factors specific to the clinic or medical office that would be performing the procedure. These include, for IVF, the live birth rate per cycle, the cumulative live birth rate after a specific number of cycles, the added success rate of subsequent frozen embryo transfer(s), and the risk of multiple pregnancy, abortion, and extrauterine pregnancy, which are compared with the success rates and risk of extrauterine pregnancy rates associated with reconstructive surgery. Significant and uncorrectable male factor infertility, which would mandate IVF, would make the latter approach preferred over attempted tubal reconstruction.

The advantages of IVF are that it avoids major surgery, has a low rate of ectopic pregnancy, and overcomes significant male factor infertility or various ovulatory defects. Cryopreservation of extra embryos may make embryos available for future attempts. However, IVF is expensive, usually not covered by health insurance, associated with an increase in the rate of multiple pregnancies and cesarean sections, and an increase in the rate of spontaneous abortion. Some patients may reject IVF for personal reasons.

Successful reconstructive surgery can provide many years during which a couple can achieve one or more pregnancies. The risk of spontaneous abortion is not increased among those who conceive after tubal surgery compared with age-matched

controls. With the exception of posterior or cornual tubal implantation, the need for cesarean section is not increased by tubal reparative surgery. The risk of an ectopic pregnancy is very low following mid-tubal reanastomosis. However, tubal reconstructive surgery is usually not covered by insurance and involves a surgical procedure (generally minilaparotomy, but in some clinics, laparoscopy) and associated minor and major morbidities.

If the chance of success from reconstructive surgery equals or exceeds the "threshold" selected by the patient, microsurgical repair is indicated. A diagnostic laparoscopy before the minilaparotomy allows assessment of the remaining distal and proximal tubal segments. Doing both procedures at the same time is safer and less expensive, and insures that reconstruction is possible. Under certain conditions, diagnostic laparoscopy is skipped and only minilaparotomy is performed.

During the diagnostic laparoscopy, the presence, location, extent, and density of adhesions, the presence and extent of endometriosis, the presence leiomyomata or ovarian pathology and finally, the amount of proximal and distal oviduct(s) available are evaluated. Hydrochromopertubation confirms that the remaining proximal portion(s) of oviduct(s) are patent and free of salpingitis isthmica nodosa that predisposes to ectopic pregnancy. If the HSG suggested obstruction at the tubocornual junction, the instillation of dye transcervically under anesthesia may determine that the cause of that finding was spasm. If obstruction is confirmed, attempts can be made to overcome the block by proximal tubal cannulation under hysteroscopic guidance [143]. Women who undergo reversal have a pregnancy rate in excess of 50% within 5 years [144]. These same investigators reported that of 969 first live deliveries which occurred in 1,898 women who had undergone reversal, 20% occurred within the first year, 40% at 2 years, and 52% at 10 years.

> The 5-year cumulative live-delivery rate was significantly lower in women who were aged 40–44 years (26%) compared with those aged 20–29 (50%). Koh and Janik demonstrated that the efficacy of microsurgical tubal reanastomosis via laparoscopy equals that of repair by laparotomy [145]. *Their work has been confirmed recently* [146].

The types of procedures are multiple and their outcomes vary considerably (Table 11.7). A combination of one of these procedures with another microsurgical repair has a lower success rate. In addition to magnification, all the principles of microsurgery should be used, including gentle tissue handling and complete hemostasis. If surgery fails, a repeat operation may not be the best option and referral for IVF should be made.

Table 11.7 Outcome of tubal reconstructive surgery

Procedure	IUP	*Live birth*	*Ectopic*
Salpingostomy by laparotomy	20–40%	18–35%	10–40%
Salpingostomy by laparoscopy	10–40%	10–30%	10–35%
Reanastomosis by laparotomy	45–80%	30–80%	2–10%
Reanastomosis by laparoscopy	50–75%	50–60%	3–30%
Tubocornual anastomosis	50–60%	30–50%	5–15%
Posterior tubal implantation	50–70%	40–60%	1–2%

Research Methods

With the exception of some recently developed methods and the newer versions of quinacrine administration, many of the following methods are of historical significance and included here to demonstrate the variety of problems encountered. The early attempts at developing an "easy" technique for tubal sterilization focused on finding a caustic agent that could be placed blindly into the uterus, find its way into the fallopian tubes, and cause tubal scarring and obstruction. Most commonly, an acorn-type device surrounding the introducer was used to prevent reflux of the caustic agent into the vagina. Unfortunately, no such safety device has been designed to prevent intraperitoneal spillage. These early techniques required a number of applications of the caustic agent into the uterine cavity and the use of some other form of contraception until bilateral tubal obstruction could be documented (usually by means of an HSG).

The more recently developed techniques utilize hysteroscopic guidance and thereby avoid the blind placement of material. Direct hysteroscopic tubal coagulation is possible, although the unexpectedly high complication rate caused the procedure to be abandoned. The worldwide need for easy, affordable sterilization continues to stimulate research efforts along these lines.

Chemical Agents

When caustic agents, such as silver nitrate in a paste, zinc chloride, formaldehyde, or 2% ethanol/formalin, were tested, bilateral tubal closure rates of only 50–70% were reported after one application, but up to 95% after six applications. Histological evidence of marked tubal necrosis was documented with most agents [147]. Unfortunately, pregnancies occurred in patients who had HSG-documented bilateral tubal obstruction. Although some HSGs documenting proximal obstruction may have done so because of tubal spasm rather than obstruction, regeneration of the epithelium and restoration of tubal patency may be the explanation. Other failures included use of the sclerosing agent sodium morrhuate and phenol when used alone as a liquid mucilage, or in a paste with atabrine, and talc.

Newer research has focused upon polidocanol, a synthetic, long-chain fatty acid that is widely used as a sclerosing agent for varicose veins [148, 149]. After preliminary studies, Jensen et al. studied the effect of a single transcervical administration of polidocanol at various concentrations with and without the use of doxycycline as a co-sclerant in baboons. Follow-up was by HSG and exposure to fertile male baboons. Only a small number of animals were treated, but most achieved bilateral tubal obstruction and of those that did, no pregnancies occurred in a 16-month follow-up period.

Quinacrine

The cytotoxic agent quinacrine has been delivered to the proximal portion of the tubes in the form of a quinacrine hydrochloride solution, in quinacrine-impregnated IUDs and as quinacrine pellets. Quinacrine sterilization remains the safest, most effective, and the most widely used (>125,000 cases) non-surgical method. The ongoing interest in quinacrine is derived from the pioneering research of Zipper [150]. When the solution form of quinacrine hydrochloride at a concentration between 125 and 167 mg/mL was delivered to the proximal oviducts, bilateral closure rates of 55, 80, and 95% were achieved after one, two, and three instillations, respectively. However, possible intravascular administration and intraperitoneal spillage with attendant local damage have limited its general acceptance.

Quinacrine-impregnated IUDs of a "T" or "Y" configuration were developed to deliver quinacrine from their lateral arms, which would be maintained in close proximity to the tubal ostia. These devices solved the problems of multiple applications and intraperitoneal spillage. In addition, they provide a back-up method of contraception while the process of tubal closure is ongoing. However, they did not improve efficacy or eliminate the need for an HSG.

Cylindrical quinacrine pellets (3.2 mm in diameter) have been used also as a method of limiting peritoneal spread. The pellets are introduced via a sterile copper T IUD introducer. Seven 36 mg pellets (total dose of 252 mg) are delivered monthly to the top fundal portion of the uterus between cycle days 7 and 10 of the menstrual cycle for 2 months. The pellets dissolve within 30 minutes, releasing quinacrine, which causes necrosis of the endometrium and endosalpinx. The former recovers within two cycles, but scar tissue forms within the intramural portion of the tubes within 12 weeks, during which time contraception is mandatory. Initial reports indicated that a bilateral tubal closure rate of 73% could be achieved [151]. This rate rose to 84% after a third insertion. Perhaps as testimony to the regenerative capabilities of the oviducts, the first-year pregnancy rate of 0.7% rises to 3.8% at 24 months but remains stable thereafter (4% at 36 months). In a 4-year follow-up study, Bhatt and Waszak reported a failure rate of 3.7% [152].

With a newer insertion technique and the administration of oral papaverine as a smooth muscle relaxer, Hieu et al. reported a major complication rate of 0.03% and a failure rate of 2.7% after 4 years [153]. However, at 5 years, the pregnancy rate was 12.9% with two insertions and 27.3% after one insertion [154]. These pregnancy rates are considerably higher than those from Chile in which the 10-year cumulative pregnancy rate was 10.7% among women who were under 35 years of age at the time of sterilization and only 3.1% for those who were older than 35 [155]. In an attempt to address the issue of relaxing both uterine and tubal musculature at the time of quinacrine administration, pellets of diclofenac or ibuprofen were placed in the uterus at the time of quinacrine pellet instillation. No improvement in tubal closure rates was detected.

Liquid quinacrine has been delivered hysteroscopically, but may reflux into ampulla and peritoneum while the contralateral oviduct is cannulated [156]. A more practical approach is the use of quinacrine rods that are delivered into the intramural portions of the oviducts under hysteroscopic guidance. Although the ease of administration and very low cost of quinacrine ($1 per procedure in Asia) have contributed to ongoing interest in this procedure, concern regarding carcinogenicity caused it to be banned by the World Health Organization in 2006, a decision challenged by Lippes [157, 158].

Tissue Adhesives

The tissue adhesives gelatin-resorcinol-formaldehyde (GRF) and methylcyanoacrylate (MCA) deserve special attention [160, 161]. Their use recognized the importance to provide complete and permanent microscopic occlusion. GRF was highly efficacious, but required a special mixing device and had the complication of peritoneal spillage. Bilateral closure rates were 66 and 89% after one and two instillations, respectively. MCA has a somewhat unique property compared with other agents, in that as it flows from the proximal to more distal oviduct, the material changes from a monomer to a polymer. The polymerized form is on the outside of the advancing stream and protects the peritoneum from injury if any should spill into the cavity, a very rare event. Cell necrosis begins within 24 hours and proceeds rapidly. By 12 weeks, the tubes are scarred and the MCA has been cleared by macrophages.

To reduce the volume of solution instilled via a small, disposable device, MCA was applied via a unique delivery system, the Femcept™ device [162]. A volume of only 0.65 mL was instilled via a 4-mm cannula. In clinical trials, bilateral closure rates were 74–80% after one application, but they rose to 90–98% after a repeat application. The cumulative pregnancy rate was 3.7% 24 months after discontinuing contraception [62, 163]. With the addition of a radio-opaque material to the MCA, some flow and polymerization properties were improved and a plain X-ray could replace an HSG to verify intratubal placement. Animal and human research continues with different cyanoacrylate molecules including delivery via tubal cannulation under hysteroscopic guidance [164, 165].

Hysteroscopic Approach

Early attempts involved blind delivery of electrosurgical energy to the uterotubal junctions [166]. Coagulation of the tubal ostia has been practiced for many decades beginning with a report by Kocks in 1878 [167]. Hysteroscopy was introduced by Pantaleoni in 1869 [168]. Under hysteroscopic guidance, electrocoagulation of the fallopian tubes was reported by Mikulicz-Radecki and Freundin in 1928 [169]. However, it was not until high-viscosity dextran was introduced as a

uterine-distending medium that good, clear visualization became easy to achieve [170]. Researchers built on the pioneering work of Rodolfo Quinones and Hans Lindemann [171, 172].

Protocols were simple. Early in the follicular phase, a paracervical block was introduced, a hysteroscope was placed, ostia were identified, a flexible 3-mm monopolar electrode was placed, and the electrosurgical generator was activated in the coagulating mode. The distal end of the electrode was shielded to prevent lateral spread of the energy. Energy was delivered in 6-second intervals until the familiar white endpoint used in laparoscopic tubal coagulation had been achieved. Surgery time was usually less than 5 minutes. The patient returned to home or work within 30 minutes, continued contraception until she had an HSG in 3 months. Bilateral closure rates were almost 90%.

Inspection of the uterine cavity demonstrated the high incidence of congenital and acquired uterine defects, perhaps explaining some of the failures of non-hysteroscopic methods [173]. Other reasons for failure include tubal spasm and thickened endometrium obscuring the tubal ostia. Steerable hysteroscopes were developed so that access to eccentrically placed tubal ostia was possible [174].

However, many complications were soon reported including peritonitis, bowel injury, and even death [175]. Most complications were delayed and related to the occurrence of pregnancies months and even years after HSGs had documented bilateral tubal closure. Many of these pregnancies were extrauterine, commonly in the intramural segment of the tube, and associated with delayed diagnosis and profound hemorrhage. Trials in the United States were discontinued.

To investigate a possible etiology for these failures, we performed laparoscopy in 20 patients with successful hysteroscopic tubal coagulation procedures as documented by HSGs [176]. To assess tubal occlusion and verify HSG findings, a dilute solution of indigo carmine was instilled transcervically. Tubal closure at the cornual portion was confirmed, but 16 of the 20 patients had developed sinus tracts and fistulae. Of the 16 patients, 11 involved only the cornual portion(s) of the uterus and seven extended into the broad ligament(s). We concluded that the amount of monopolar energy delivered in the original hysteroscopic tubal coagulation far exceeded what was expected. Additionally, lateral spread and a “burst effect” (when the generator is set in the coagulating mode) caused excessive damage to the intramural portion of the fallopian tubes. Although the procedure had successfully interrupted the fallopian tubes, extensive damage had been done and the regenerative powers of the tubes resulted in channel and fistulae formation, and resultant extrauterine pregnancies. The procedure became one of historical significance only.

The Brundin P-Block

The Brundin P-block consists of a hydrogel of polyvinyl pyrrolidone and methylacrylate on a nylon skeleton, which allows both expansion of the device after placement and tissue in-growth. The device is small (1.4 mm in diameter × 4 mm long)

and held in place after placement by two 2-mm anchoring wings. However, only 49% of the patients achieved bilateral tubal closure *and thus* the device cannot be considered "sterilizing" [177]. The final modification of the device, Mark 9, was only somewhat more efficacious [178].

Hosseinian Uterotubal Junction Device

The Hosseinian device is a 1-cm-long polyethylene device [179]. It is 1 mm in diameter at its intramural side but 2 mm in diameter at its base where four 5.2-mm spines are attached by a screw. These spines were designed to anchor the device in place. Non-reactive materials were used in the hope that removal would restore fertility. However, neither high levels of tubal occlusion nor reversibility could be demonstrated and trials were discontinued.

Hamou Intratubal Thread

The Hamou intratubal thread was designed to be reversible and minimize or avoid damage to the tubes [180]. The device consisted of a 28- to 30-mm-long- × 1-mm-in-diameter nylon thread. At each end of the thread was a loop that prevented migration of the device into the uterus and the peritoneum. The loop on the uterine side also could be used for removal via hysteroscopy. Of 166 patients, 156 (94%) had successful placement. After 1 month, there were four expulsions proven by hysteroscopy, and after 1,471 cycles, there was one intrauterine pregnancy. However, as with all methods, "sterilization" requires complete tubal obstruction.

Rigid Plugs

A rigid 7 mm × 2 mm 3-M ceramic plug was designed to provide complete tubal occlusion via a reaction to the porous α alumina [181]. Premolded silicone devices were provided with or without a central metal core. For reversible sterilization, a 10 mm × 1.5 mm notched device was developed, but it was neither efficacious nor reversible [182]. The incidence of expulsions caused by contractions of the muscular intramural portion of the oviduct and perforations secondary to the convoluted course of the intramural segment were high.

Formed-in-Place Silicone Plugs (Ovabloc)

Formed-in-place silicone plugs were another novel concept and appeared to have a bright future [183, 184]. As with other hysteroscopic approaches, follicular phase timing and normal anatomy were prerequisites. Procedures were completed in less

than 30 minutes under paracervical block anesthesia. Unlike the rigid silicone plugs used in previous trials, the shape of these plugs was customized to the anatomy of each individual oviduct. After a tubal ostium was identified, a catheter with an obturator tip was passed through the operating channel of the hysteroscope. The obturator tips were hollow and of varying shapes to conform to different ostial configurations. Liquid silicone was mixed with its catalyst, stannous octoate, and instilled into the catheter. The flow of silicone continued and an exact mold of the oviduct was created from the proximal oviduct to the ampulla. Tiny amounts of elemental silver within the liquid silicone allowed the operator to monitor flow of the silicone–catalyst mixture and made the plugs radio-opaque. An immediate postoperative X-ray and another in 3 months could ensure proper placement, configuration, and that the distal plug remained bonded to the obturator tip. Because these plugs were larger at both ends, a properly configured plug should be larger at both ends than in the middle and thus would be "locked" into place. Placement of plugs on both sides was successful in 90% of patients and in 90% of these patients, the plugs were normal providing an unacceptably low success rate of 81% [185]. Moreover, if the plugs migrated into the peritoneum, adhesion formation occurred. This device was removed from the US market in 2009.

Neodymium-Yttrium-Aluminum-Garnet (Nd:YAG) Laser

Because of the high power and significant later spread of energy, the Nd:YAG laser would appear to be an ideal device to achieve tubal occlusion under hysteroscopic guidance. The laser energy is delivered via a long, flexible, quartz fiber, and applies thermal energy to tissue at a depth of 5 mm. However, a trial of its efficacy was terminated after only 17 patients were treated because of a tubal patency rate of 74% [186].

Intratubal Ligation Device

The intratubal ligation device is still in an early stage of development. The overall approach involves placement of a catheter system into the lumen of the fallopian tube, invagination of a portion of the endosalpinx, and ligation of the resulting pedicle with an elastomeric band. Sterility is achieved immediately via band placement over the tubal lumen and thus it differs from all other hysteroscopic methods in a most important way.

This device consists of a triple layer of coaxial catheters made of extruded nylon. The retracted tip of the inner catheter forms a deflated balloon, the middle lumen has an expanded tip that houses an O-ring, and the outer catheter pushes the O-ring over an invaginated tissue pedicle of endosalpinx. During insertion, the leading tip of the device is approximately 1 cm of double-hulled silastic tubing that reduces the risk of perforation during insertion and serves as the inflatable balloon during device deployment. The device is advanced into the tubal ostium and tubal lumen until the

isthmic-ampullary junction has been reached. The balloon is inflated and a minimal amount of methylcyanoacrylate is delivered through the pores in the outer balloon. Adherence occurs on contact. The balloon is deflated and the adhered tissue is withdrawn slowly toward the second lumen. Further retraction of the expanded tip envelopes the invaginated tissue and the O-ring is deployed over the tissue, sealing the oviduct. Following tissue necrosis and sloughing, long-term contraception is achieved by means of localized scarring.

Although work with this procedure is in preliminary stages, it is an exciting concept and its unique property of immediate effectiveness is a most important milestone for hysteroscopic sterilization.

Microwave Sterilization

Microwave energy has been used successfully to cause endometrial ablation [187]. If trials using modified devices demonstrate safety, studies may begin perhaps with delivery of the microwaves under ultrasound guidance.

Reversible Hysteroscopic Sterilization

Xu et al. have begun research using a nickel-titanium shaped memory alloy which, following placement, opens like an umbrella providing complete tubal obstruction [188]. The device is placed while being immersed in low-temperature distention fluid and is deployed when its temperature rises to that of the patient's body temperature. This device is unique, in that it is effective immediately, does not damage the intramural portion of the fallopian tube, and is reversible. Hopefully, animal trials and thereafter human trials can begin.

Conclusion

The development of a safe and effective hysteroscopic sterilization procedure is a high priority. In a review of more than 105,000 patients who underwent surgical sterilization in France (two-thirds by a hysteroscopic procedure and one-third by a laparoscopic technique), Bouillon et al. reported that although the risk of surgical complications during surgery was less for those who underwent a hysteroscopic approach (0.13% vs. 0.78%), failure rates after 1 year (4.83% vs. 0.69%) and 3 years (5.75% vs. 1.29%) were higher among those in the hysteroscopy group as were rates for reoperation during the first year (5.65% vs. 1.76%) [189]. The risks of general medical complaints were not significantly different. In contrast, Perkins et al. compared the outcomes of more than 42,000 women who underwent laparoscopic sterilization to those of almost 28,000 whose sterilization was performed

Table 11.8 Today's methods of sterilization versus the ideal method

Parameter	*Ideal*	*PS*	*LTC*	*LTB*	*BTC*	*Salp*	*HSC*
Skill/training	Minimal				+		
Paramedic procedure	Yes				+		
One treatment	Yes	+	+	+		+	+
Effectiveness	High	+	+	+		+	+
Effective immediately	Yes	+	+	+		+	
Office procedure	Yes				+		+
Anesthesia	None, local				+		+
Minimally invasive	Yes				+		+
Pain	Minimal		+	+	+		+
Rapid recovery	Yes				+		+
Ideal for high risk patient	Yes				+		+
Morbidity	Minimal	+	+	+	+		+
Mortality	None	+/−	+/−	+/−	−		−
Patient privacy Equipment needed	Maximum Little				+ +		+ +
Reusable equipment	Yes	+	+	+/−			+/−
Equipment maintenance	Minimal	+			+		
Visible scar	None				+		+
Possible during pregnancy	Yes	+	+/−	+/−		+	
Possible postpartum Possible post-abortion	Yes Yes	+ +	+	+		+ +	
Inexpensive	Yes				+		+/−
Reduce/prevent STDs	Yes					+	
Reversible	Yes	+	+/−	+			+/−

PS partial salpingectomy (at cesarean section, interval, abdominal or vaginal), *LTC* laparoscopic tubal coagulation (monopolar or bipolar), *LTB* laparoscopic application of band or clip, *BTC* blind transcervical, *Salp* salpingectomy, *HSC* hysteroscopic

hysteroscopically. Although more women in the hysteroscopic group had menstrual dysfunction and underwent further hysteroscopic procedures, fewer complained of pelvic pain and fewer underwent subsequent abdominal surgeries [190].

Table 11.8 compares various methods of sterilization available today. Although we are still somewhat removed from the ideal, transcervical approaches remain the most attractive because of ready access to the fallopian tubes, safety, and the fact that they can be performed with minimal anesthesia.

Suggested Reading

Camara S, de Castro Coelho F, Freitas C, et al. Essure present controversies and 5 years' learned lessons: a retrospective study with short- and long-term follow-up. Gynecol Surg. 2017;14:20–5.

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Gannon M, Collins C, Crinion D, et al. (2017) AltaSeal treatment for hydrosalpinx before in vitro fertilisation. Presented at the RCOG World Congress 2017 In Cape Town, South Africa, 20–22 March 2017.
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Thurkow AL. Hysteroscopy and contraception: an overview. Chap. 31. In: Tinelli A, Pacheco LA, Haiimovich S, editors. Hysteroscopy. Switzerland: Springer; 2018. p. 302–14.
Of the 19 women with unilateral or bilateral hydrosalpinges, 18 had successful placement of the AltaSeal device prior to undergoing in vitro fertilization. Tubal obstruction was proven by HSG 1 day and again 12 weeks after hysteroscopy. 8/18 women conceived (26% of IVF attempts) and 7 delivered.
Of the 18 women undergoing a total of 31 IVF cycles after AltaSeal insertion, 8 (45% of women and 26% of IVF cycle attempts) conceived and 7 delivered live births (39% women and 23% of IVF cycle attempts.

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Chapter 12
Behavioral Methods of Contraception

Anna L. Altshuler and Paul D. Blumenthal

Introduction

A large proportion of couples rely on behavioral methods of contraception, at least intermittently or at some point in their lives. These methods rely on knowledge about male and female reproductive physiology and the menstrual cycle rather than medications, herbs, devices, or barriers to prevent pregnancy. Behavioral methods can be divided into two categories: methods that do not rely on the menstrual cycle (i.e., abstinence or *coitus interruptus*) and methods that rely on the menstrual cycle. Methods that rely on the menstrual cycle can be further subdivided into Fertility Awareness Methods (FAM) and "Natural" Family Planning (NFP). FAM includes methods that rely on women to monitor physiologic changes during their menstrual cycle whereas NFP relies on the menstrual calendar to distinguish likely fertile from nonfertile days.

All behavioral methods of contraception require the couple to modify their sexual behavior in some way. Many couples use a variety of different menstrual-cycle-dependent or menstrual-cycle-independent techniques such as avoiding sex (also known as "periodic abstinence") or using withdrawal with coital acts. Barrier methods (Chap. 11) are also commonly used in combination with FAM. Behavioral methods of contraception are critically important for many couples for whom this is the only religiously, culturally, or socially acceptable way to prevent pregnancy. This chapter provides information about techniques that can enhance the success of each of these methods.

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Behavioral Method Options: Methods Independent of the Menstrual Cycle

General Overview

Abstinence and *coitus interruptus* are the two methods that do not rely on the menstrual cycle, medicines, devices, or barriers to prevent pregnancy. They may be used as the exclusive method to prevent pregnancy or in conjunction with other methods.

Abstinence

Worldwide, it has been estimated that 200 million reproductive-aged women use abstinence as their method of birth control, where abstinence is defined as the avoidance of penile-insertive vaginal intercourse. For some women and men, this is a permanent choice, but for others it may be a temporary one. This latter situation accounts for the variable success rate of abstinence. If practiced, abstinence should be 100% effective, but when used as a method at one point of time but not practiced consistently, "abstinence" carries with it a measurable risk of pregnancy, with failure rates as high as not using any method at all.

Candidates and Counseling

Individuals who find sexual pleasure through means other than penile-vaginal intercourse and feel empowered to negotiate the type of sex they have are good candidates for abstinence to prevent pregnancy. However, circumstances may change in a sexual relationship making abstinence no longer appropriate. Moreover, individuals may have other considerations besides pregnancy prevention such as sexually transmitted infection (STI) prevention. Individuals who abstain from penile–vaginal intercourse but engage in penile–oral, vaginal–oral, anal–oral, or penile–anal sex are at risk for STIs. It is important for physicians to be aware of these practices so that they can advise patients appropriately about possible health implications and prevention strategies and can test more successfully for STIs.

Adolescents and Abstinence Programs

Considerable effort has been invested in developing programs to encourage abstinence among adolescent men and women, usually referring to abstinence from all sexual activity (including oral and anal intercourse). The benefits are obvious: total

abstinence provides the only truly effective way to prevent pregnancy and possibly STI prevention, depending on the individuals' specific sexual practices. Abstinence can help promote self-esteem and maintain a young person's options for self-growth and financial self-sufficiency. In the United States, about 30% of adolescents initiate sex between the ages of 15 and 16 and the percentage rises to 50% for adolescents between the ages of 17 and 18 [1]. The majority of younger adolescents practice abstinence and the occurrence of sexual activity among adolescents less than 12 years old is likely to be nonconsensual [1].

Experience with a wide variety of abstinence-promoting programs has provided important insights. Programs based on a "just say no" approach or that threaten young women with STIs or unintended pregnancies if they engage in sexual activity ("scare them straight" approach) have been shown to have no effect on either sexual behavior or contraceptive use [2]. On the other hand, comprehensive sexual education programs that combine abstinence, condom and contraceptive education do not encourage promiscuity among adolescents and have positive behavioral effects such as a delay in initiation of sex, reduction in number of sexual partners of frequency of intercourse, and an increased use of condoms and contraception [3].

Coitus Interruptus

Coitus interruptus, or withdrawal, requires that the penis be removed from the vagina and directed away from the external genitalia of the woman before ejaculation to prevent sperm from entering the upper reproductive tract and fertilizing an ovum. Historically, *coitus interruptus* has been an important method. In the United States, official estimates from the 2006–2008 National Survey of Family Growth are that 5% of women rely on this method for contraception [4]. This practice is more common among younger women as 31% of women 15–24 years of age reported using the withdrawal method [5].

Effectiveness

Coitus interruptus is more effective than is generally perceived; it is roughly equivalent to typical use of some female barrier methods. It is not a substitute for condoms if intending to prevent sexually transmitted infections and HIV.

Clinical trial data are not available to calculate the failure rates for consistent and correct use, although some experts have estimated that the failure rate should be approximately 4% with perfect use. Typical-use first-year rates have been measured to be 18% [4]. The benefits of this method are obvious: it requires no drugs or devices; it does not interfere with foreplay or precoital spontaneity; and it is readily portable and available.

Candidates

Coitus interruptus relies on the male partner to be able to sense impending ejaculation, resist the involuntary urge for continued deep thrusting and withdraw before ejaculation. Coital positioning is also important. Unless the couple is effectively able to communicate in time to permit the woman to move, the male superior position or at least a male-controlled coital position is necessary.

Noncontraceptive Benefits

Coitus interruptus may have some protective effect in lowering HIV transmission among HIV-discordant heterosexual couples [6]. Nevertheless, HIV can be in pre-ejaculatory fluid, making condoms a more effective way to prevent HIV than *coitus interruptus*. Withdrawal does not appear to protect against other sexually transmitted infections, and ulcerative lesions on the genitals, in particular, increase the risk of HIV transmission.

Drawbacks

With *coitus interruptus*, the dynamics of intercourse are disrupted. Researchers have reported mild to extreme clouding of consciousness just before ejaculation; deep thrusting motions are involuntarily triggered in many men with impending ejaculation [7]. Interruption of penile–vaginal contact at this phase of the sexual response curve may decrease the intensity of the male orgasm. Similarly, for the woman who may be at another phase of sexual arousal, complete cessation of all penile stimulation may not only diminish pleasure but also result in frustration.

Patient Education

Minimal instructions are necessary, but the man should know he must urinate and wipe off the tip of his penis before intercourse to remove any sperm lingering from a recent ejaculation. Most importantly, he must learn how to completely withdraw his penis and direct it away from the woman's genitals before ejaculation.

As with any barrier or behavioral method, emergency contraception should be provided to the couple to have readily available should the woman have an accidental exposure to sperm. It is also strongly advised for both partners who are new to each other to be tested for sexually transmitted infections before initiating this method.

Behavioral Method Options: Methods Dependent on the Menstrual Cycle

Fertility awareness methods (FAM) and natural family planning (NFP) methods all depend on determining when a woman is fertile, as depicted below, and avoiding the possibility of fertilization on those days, either by not having penile–vaginal intercourse, practicing withdrawal, or using a barrier. Between 2006 and 2008, it was estimated that 25% of women had used one of these methods as contraception at some point in their lives [4]. Successful use of these methods depends on a couple's understanding of reproductive physiology. The National Campaign to Prevent Teen and Unplanned Pregnancy surveyed unmarried 18–29 year olds in the United States and found that 40% of those relying on behavioral methods of contraception did not know when a woman's most fertile time of the month was [8]. Furthermore, the fertile window can be variable, even in women who have regular menstrual cycles, making it difficult to be certain when one is at risk for pregnancy [9].

Candidates

Only women with regular menstrual cycles may be appropriate candidates for contraceptive methods that rely on timing with the menstrual cycle. Women who should be offered more effective methods are those with polycystic ovary syndrome or transitioning to menopause or use medications or herbs that affect their menstrual cycle. Success requires that both members of the couple agree to abstain or use protection during the data collection periods and during the at-risk days. In clinical trials, the greatest source of failures has been that couples decide to have intercourse despite clear indications of ovulation [10]. Given such realities, users should be extensively counseled about emergency contraception and ways to obtain it.

Effectiveness and Continuation Rates

Typical use failure rates are reported to be 25%. The typical use failure rates vary little among the currently available methods, mostly because of routine violation [11]. However, failure rates associated with consistent and correct method use do vary, depending on whether pre-ovulation intercourse is permitted or excluded. The calendar method has a 9% failure rate with correct and consistent use, compared with 3% for ovulation detection, 2% for symptothermal method, and 1% for post-ovulation method [12]. Continuation rates with FAM and NFP methods in well-supported programs after 1 year range between 52% and 74% [12].

Specific Methods to Detect Ovulation: Natural Family Planning

Calendar or Rhythm Method

Several techniques have been developed to identify fertile days by using a calendar and physiologic changes women experience during the menstrual cycle. For the "calendar" or "rhythm" method, it is assumed that sperm last 1–3 days in the genital tract and an egg is vulnerable to fertilization up to 24 h after ovulation. The fertile window includes, at least, the 5 days before ovulation and the day after (total of 6 days). To use this method using traditional approaches, it is necessary to obtain information about the woman's spontaneous menstrual cycling for at least 6 months. The first day of abstinence is calculated by subtracting 18 from the number of days in the woman's shortest cycle. The latest day of her fertile period is calculated by subtracting 11 from the number of days in her longest cycle. Tables such as Table 12.1 can be consulted to confirm the calculations. For example, a woman whose 6-month data showed that her cycle length varied between 26 and 30 days would be required to abstain from coitus between days 8 and 19 each month; the couple may engage in intercourse on cycle days 1–7 and from day 20 to menses.

The need to document cycle lengths was highlighted in a prospective study of low-literacy Mayan women who were self-declared to be "regularly cycling." Quite surprisingly, only 46% of these women were found to have regular cycles (26–32 days), even for three consecutive months [13]. Clearly, approaches such as blanket days 9–19 of abstinence will result in higher than expected failure rates when such dramatic inherent variation in cycle length exists. The traditional calculation requires an average of 13 days of abstinence a month for the general

Table 12.1 Calculation of fertile period

Shortest cycle (days)	First fertile (unsafe) day	Longest cycle (days)	Last fertile (unsafe) day
21	3	21	10
22	4	22	11
23	5	23	12
24	6	24	13
25	7	25	14
26	8	26	15
27	9	27	16
28	10	28	17
29	11	29	18
30	12	30	19
31	13	31	20
32	14	32	21
33	15	33	22
34	16	34	23
35	17	35	24

Day 1 = First day of menstrual bleeding. (Adapted from Ref. [11] Hatcher)

population and provides 67.8% coverage of peak risk days [14]. Even when women have regular cycles, they may ovulate earlier or later than expected using these calculations. In one study of 221 healthy women attempting to conceive, 10% of women with regular cycles were in their fertile window on any given day between days 6 and 21 [9].

Standard Days Method Using CycleBeads® (NFP)

The standard days method was developed by Georgetown University investigators particularly for women desiring to start a simple method immediately and for those with low literacy [15]. It is designed for women who have cycle lengths lasting 26–32 days. Women are given CycleBeads® (Figs. 12.1 and 12.2), a device designed to assist women in monitoring their cycles and determining their fertile days. A smartphone Cyclebeads® app with the same purpose is also available. The first bead is red, which represents the first day of menses. The next six beads are brown, representing nonfertile days. Fertile days are represented by the following 12 white beads, which are followed by another 13 brown "infertile" beads. The patient advances a moveable ring one bead a day to determine her fertility. The at-risk white beads even glow in the dark. There are two black beads at days 27 and 32. If the woman's menses starts before she reaches the first bead, then she learns that her cycle length is too short to rely on the CycleBeads®. Similarly, if she reaches the 32nd (black) bead without having started her menses, her cycle is too long to use the standard days method. A backup calendar is provided to allow for the woman to record that she has moved the elastic band every day as directed. CycleBeads® can be purchased online or users can get a phone application instead of the physical beads. One study of women using this technique in the Philippines, Peru, and Bolivia found a first-year pregnancy rate of 4.8% with correct use, meaning no intercourse days 8–19 of the cycle. Of the participants in this study, 28% had two

Fig. 12.1 CycleBeads®. (Courtesy of Cycle Technologies; www.cyclebeads.com)

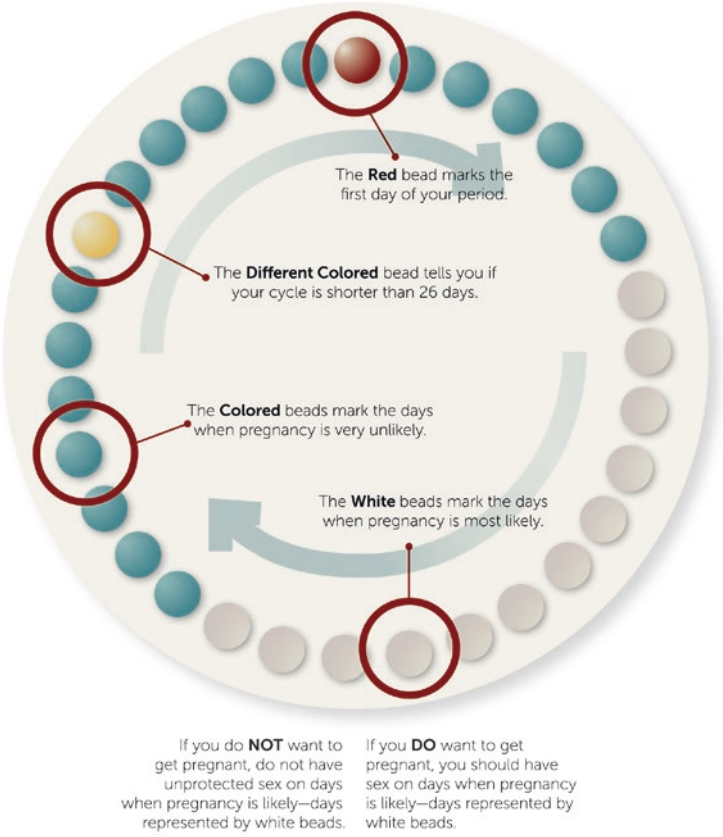

Fig. 12.2 CycleBeads®. (Courtesy of Cycle Technologies; www.cyclebeads.com)

cycles out of the 26 to 32-day range and were excluded from the results. The probability of pregnancy was 12% with typical use [16].

Specific Methods to Detect Ovulation: Fertility Awareness Methods

Basal Body Temperature Method

Other techniques are available to predict ovulation. Basal body temperature (BBT) measurements are used to detect ovulation and, more importantly, to indicate when the risk of pregnancy has passed for a given cycle. Patients are instructed to measure

their temperatures at the same time each day before arising. There are dedicated thermometers on the market to measure BBT. Ovulation is identified by an average temperature increase of about 0.4–0.8 °F (usually following a slight dip in BBT). Studies have shown that ovulation occurs within 48 h of either side of the temperature shift. Inaccuracies in measurements may be introduced if the woman gets out of bed at night, has an infection, or varies the time of day the temperatures are taken. Intercourse is not allowed for at least 3 days following the temperature rise. However, this does not protect against exposure to semen when intercourse immediately precedes the BBT rise. In practice, only 80% of women have interpretable BBT patterns. Therefore, the best use of BBT is as a post-ovulatory method or in combination with some other technique that can better predict ovulation.

Cervical Mucus Methods

Billings Technique

The Billings technique of ovulation detection relies on changes in cervical/ vaginal secretions that reflect the hormonal swings of the menstrual cycle. Each day, the woman touches a piece of paper or her finger against her vaginal opening before urination to test the quantity and character of those secretions. During the days following menses, cervical mucus is scant and the vaginal testing will be negative. As the follicular phase advances, the secretions increase slightly, but they are still viscous. The pre-ovulatory estrogen surge dramatically increases the amount of these secretions and makes them clearer and more elastic (creating the maximal finger-to-thumb Spinnbarkeit sign) [17]. After ovulation, the mucus again thickens under the influence of progesterone, and coitus may be permitted only after 3 days of dry secretions.

A woman wanting to use the Billings method must first learn about her cycles. Data are best gathered during a period of 6–9 months of abstinence. After a woman learns how to interpret her mucus patterns, the couple should forego coitus at least every other day to permit a woman to assess her fertility without having her measurements confused by seminal fluid or vaginal secretions resulting from the woman's own sexual arousal. Other external factors can also confound these measurements. A woman's vaginal moisture may be changed by vaginal infections or vaginal therapies. Douching may result in misreading, either directly—by eliminating important evidence—or indirectly, by disrupting her vaginal defense system and inducing vaginal infections.

Two-Day Method

A simpler technique using cervical secretions, called the two-day method, has also been proposed. A woman relies on the presence or absence of cervical secretions to determine whether or not she is fertile each day, asking herself, "Did I note secretions

today?" and "Did I note secretions yesterday?" She considers herself fertile if she notices cervical secretions of any type on that day or the day before, avoiding intercourse on these days. The first-year pregnancy rate in one study using this method was 3.5% with correct use of the method and 13.7% with typical use, with 96.4% of participants saying that they had no difficulty in detecting secretions after the third cycle. The mean number of days with secretions was 12.1, which is comparable with the standard days method [18]. This method can be started at any time in the cycle as opposed to the first 7 days of the cycle as was first assumed [19].

Symptothermal Technique

A more effective method of ovulation detection is the symptothermal technique, which combines at least two of the above techniques and may add other potential signs and symptoms to detect ovulation. Experienced patients may check the cervix for changes in texture, dilation, and position (at ovulation the cervix softens, moistens, dilates, and elevates in the vagina). In addition, clues about ovulation may come from changes in libido or the discomfort of Mittelschmerz. Effectiveness of this method has been 2–3% failure among perfect users and as high as 20% failure among typical users [15].

Having used any of these methods to detect ovulation, couples may use different strategies to prevent pregnancy. Intercourse can be permitted only after all risk of ovulation has passed (i.e., the post-ovulatory approach) or it may also be permitted at times when the risk of impending ovulation is minimized (e.g., the dry, scant mucus days immediately after menses). Sperm have been noted to survive in the vagina for 7 days. None of the available methods can anticipate ovulation 1 week in advance.

Technology

Apps

Apps installed on a personal device, such as NaturalCycles™, DOT Fertility Tracker™, Clue™, or Spot On™, can help organize data related to the menstrual cycle to predict both fertile and nonfertile days. Some apps are free and others require a subscription for purchase for enhanced functionality. Users are asked to input information about their menstrual symptoms, cervical mucus, basal body temperature, and intercourse. The apps use algorithms to interpret data and guide users in timing intercourse and becoming more knowledgeable about their bodies. Some apps sync with relatively expensive devices that detect basal body temperature such as the Ava™ bracelet and the Kindara Wink™ oral thermometer.

Theoretically, apps should diminish user error (having to write down data or remembering it) and allow the user to compare multiple metrics over time. One study has shown

a fertility tracking app using calendar method and mentrual cycle data to be highly acceptable among users [20]. Some apps are more intuitive than others and they vary in degree of scientific accuracy [21]. Of the many apps available, NaturalCycles™ has been cleared by the Federal Drug Administration as a contraceptive method and, along with DOT Fertility Tracker™, has been more rigorously studied than other apps [22–24].

Fertility Detection Products

Handheld fertility detection monitors, also known as electronic hormonal fertility monitors (EHFM) provide ongoing analysis of a woman's vulnerability to pregnancy. These devices were originally designed for women to use to achieve pregnancy but can also be used with contraceptive intent. Each day a woman uses the fertility monitor to check her fertility status. Different monitors employ different mechanisms to differentiate between fertile and nonfertile days such as detecting urinary metabolites of luteinizing hormone and estrogen (estrone-3-glucuronide), basal body temperature via body-worn sensors (including vaginal sensors), electrolyte composition in the saliva, and other data entered by the user.

Clearblue® makes two monitors using the same techonology, one designed to prevent pregnancy called Persona™ and an ovulation monitor called Clearblue. Persona is only available for purchase online. The ovulation monitor is designed to be used by couples desiring to become pregnant and not approved as a contraceptive. It instructs the woman to start using test strips that detect LH and estrone-3-glucuronide in her urine. The test strip is inserted into the monitor, and the monitor determines whether there is low, high or peak fertility. Use of monitors designed to help achieve pregnancy results in a period of abstinence shorter than those recommended with cervical mucus or calendar methods, which may result in higher failure rates because they may not provide enough time before ovulation to avoid intercourse. Alone, monitors are effective 94% of the time at preventing pregnancy [25]. It has been postulated that, if used in conjunction with cervical mucus screening and/or basal body temperature, they might be more effective at preventing pregnancy. The Marquette method, combining a fertility monitor with cervical mucus and basal body temperature, has been studied and this approach is feasible and improves efficacy [25, 26]. The cost of a fertility monitor and monthly supply of test sticks may be cost-prohibitive to use for a prolonged amount of time. Consumers may also purchase ovulation predictor digital tests or test strips for a fraction of the cost of monitors. These products detect LH urinary metabolites and turn positive during the LH surge. A pilot study has compared using an ovulation predictor kit plus FAM to a FAM-only method to aid users in identifying infertile post-ovulation phase of the menstrual cycle [27]. The combined use of both methods appeared to help women identify the luteal phase more accurately.

The OvaCue™ fertility monitor is an alternative to urine-based methods that measures electrolyte changes in salivary and cervical mucus and uses an oral and vaginal sensor to determine degree of fertility during the cycle. It detects ovulation with 98%

accuracy and appears to predict ovulation more in advance compared to urine-based methods. Lastly, there are ovulation saliva tests (Fertile-Focus™ and several others) that require the user to put her saliva on a glass slide and look at the pattern using a small microscope. A distinct fern pattern of the saliva, influenced by rising estrogen levels, predicts ovulation in the next 72 hours. A comparison of microscopes and home fertility monitors found neither to be as effective as the symptothermal method; microscopes had a high false-negative rate for fertile days [28].

Benefits

Advantages of FAM/NFP are wide ranging: no exogenous devices or drugs are routinely used, most couples learn a great deal about their own reproductive physiology, and it may be the only method accepted by various religious and cultural groups. The same techniques for identifying at-risk days can be used by couples seeking pregnancy to conceive. There are no direct medical side effects from use of the method, although the psychosocial implications of avoiding and planning intercourse for significant periods of time should be taken into account by couples considering use of these methods.

Training

With the exception of the standard days method with CycleBeads®, couples need extensive formal training to effectively practice periodic abstinence or fertility awareness. There are many community resources available to provide more detailed education. The organizations listed in Table 12.2 can provide advice, charts, and teaching plans.

Postpartum Women: Lactational Amenorrhea

During the postpartum period, the hypothalamic–pituitary–ovarian axis is temporarily suppressed. Lactation temporarily raises prolactin, which blocks activation of the axis. Amenorrhea induced by breast-feeding in the first 6 months postpartum is a relatively accurate clinical marker of ovulation suppression. During the first 6 months postpartum, the first menses a woman experiences (if she has a period) is usually anovulatory bleeding; menstrual bleeding usually precedes ovulation. Being forewarned, a woman can utilize other contraceptive methods to protect herself after such a menses against future, probably ovulatory, cycles. After 6 months of postpartum amenorrhea, however, the first cycle is usually ovulatory. This places the woman at risk for an unannounced return of fertility if she relies exclusively on the lactational amenorrhea beyond 6 months. Lactational amenorrhea method (LAM) refers to women who are

Table 12.2 Behavioral methods of contraception resources for advice, charts, teaching plans, and referrals

Billings ovulation method association, BOMA-USA Website: http://www.boma-usa.org
The couple to couple league international Website: www.ccli.org
Fertility awareness center Website: http://www.fertaware.com/
The global library of Women's medicine
Chapter: Fertility awareness methods of family planning for achieving or avoiding pregnancy
Website: http://www.glowm.com/
Fertility instructor Website: http://www.fertilityinstructor.com/
Institute for Reproductive Health Website: http://irh.org/
Marquette University natural family planning Website: http://nfp.marquette.edu/

intentionally informed and supported to use breast-feeding for contraception, rather than something that just happens physiologically. LAM does not appear to be more effective in preventing pregnancy than exclusive breast-feeding and amenorrhea per a Cochrane Systematic Review [29].

The criteria for lactational amenorrhea have changed over time. Early World Health Organization studies included only women who were amenorrheic, breast-feeding on demand, and offered no other source of suckling to the infant. Women were still considered amenorrheic if uterine sloughing occurred within 56 days postpartum as bleeding during this time does not correlate with return to ovulation [30]. Exclusive breast-feeding was defined as an infant receiving at least 90% caloric intake via breast milk. Later studies abandoned the need to exclude pacifiers. Most recently, studies have clarified the two most important predictors of protection from pregnancy: amenorrhea and time since delivery. In amenorrheic women who were fully or partially breast-feeding, pregnancy rates were 1% in the first 6 months. However, pregnancy rates rose to 4–7% by 12 months. Interestingly, there was no difference in pregnancy rates between partially or fully breast-feeding women [31]. All the studies demonstrated the need to provide added protection after 6 months, even if the woman remains amenorrheic while breast-feeding.

Candidates

Breast-feeding women who remain amenorrheic may practice lactational amenorrhea as their only method for up to 6 months postpartum. However, some women may not be able to breast-feed for medical or social reasons. An HIV-infected woman should

avoid breast-feeding if other sources of nutrition are available to her infant. Similarly, women taking drugs that cross into the breast milk and may harm the baby should not breast-feed. Breast-feeding requires privacy and continuous accessibility of the mother to her child. Working mothers may not have that opportunity, although breast pumping and milk storage for later consumption is a possibility for some women.

Noncontraceptive Benefits

Breast milk is best suited to meet the nutritional requirements of the human infant. Breast-fed children have fewer gastrointestinal problems and decreased rates of allergies and asthma later in life. The mother–child bond reinforced by breast-feeding is also very important. The convenience of the temporary protection offered by lactational amenorrhea in women already dedicated to breast-feeding can be very attractive at this busy time in a woman's life. Epithelial ovarian cancer rates are reduced in women who breast-feed before age 30 years [32]. Breast cancer rates are not affected by lactation unless it is continuous for at least 2 years.

Drawbacks

Breast-feeding may be perceived as embarrassing or inconvenient by some women. Cracked nipples, mastitis, and even breast abscesses are possible complications of breast-feeding. The hypoestrogenic state induced by lactational amenorrhea may decrease vaginal lubrication and cause dyspareunia. Most of these side effects, however, result from breast-feeding alone. The decision to use LAM for birth control can be viewed as an independent decision not adding any additional side effects. It must be remembered that lactational amenorrhea does not offer any protection against STIs. This is particularly important during the first week postpartum, when an STI could easily result in upper tract infection. The hypoestrogenated vagina may also be more vulnerable to HIV infection.

Summary

Total sexual abstinence is the most effective method of birth control, but incomplete commitment can result in high rates of unintended pregnancies. *Coitus interruptus* has failure rates similar to the female barrier methods. Periodic abstinence and fertility awareness methods rely on menstrual calendars, CycleBeads®, BBT, changing cervical mucus, or the symptothermal method to detect at-risk fertile days. Lactational amenorrhea is very effective for up to 6 months postpartum. All of these methods rely on a highly motivated couple who understand reproductive physiology and are willing to modify their sexual behavior to prevent pregnancy.

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Chapter 13
Male Permanent Contraception: Vasectomy

Jasmine Patel and Barton H. Wachs

Introduction

Women's health providers who counsel couples desiring permanent contraceptive methods should include recommendations for the use of male permanent contraception, via vasectomy. Vasectomy is a quicker, safer, more effective, and more cost-effective method of permanent contraception than female methods, such as bilateral tubal ligation or salpingectomy.

Despite these advantages, vasectomy is underutilized as a contraceptive method in the United States. According to the National Survey of Family Growth, only 4.5% of women aged 15–44 years relied on vasectomy for contraception between 2011 and 2015 [1]. In comparison, 13.4% of women aged 15–44 years have undergone tubal ligation during the same time period [2]. Disparities in the use of tubal ligation over vasectomy are more pronounced in the United States compared to Canada and the United Kingdom, where vasectomy use is equal to or more frequent than tubal ligation [3]. A survey of 400 couples on permanent contraceptive preferences found that vasectomy was chosen when (1) it was believed to be "easier" than tubal ligation, (2) the physician recommended a vasectomy, (3) there was effective

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couples' communication, and (4) the couple was previously relying on condoms for pregnancy prevention; these factors may be facilitated by couples' counseling that can be provided by obstetrician-gynecologists (OB/GYNs) [4]. In another study of 84 couples who chose vasectomy for permanent contraception, their primary reported reasons included favorable reports from other men (40%) and recommendations by general practitioners (21%) [5]. Therefore, women's health providers may play an important role in vasectomy uptake by including the method in their permanent contraceptive counseling. Additionally, a growing number of family planning providers are receiving training to be able to directly offer this procedure [6].

Mechanism of Action

Vasectomy severs and/or occludes the vas deferens, disrupting the passage of sperm during ejaculation. Given sperm are produced throughout a man's lifetime, vasectomy provides lifelong contraception (Fig. 13.1).

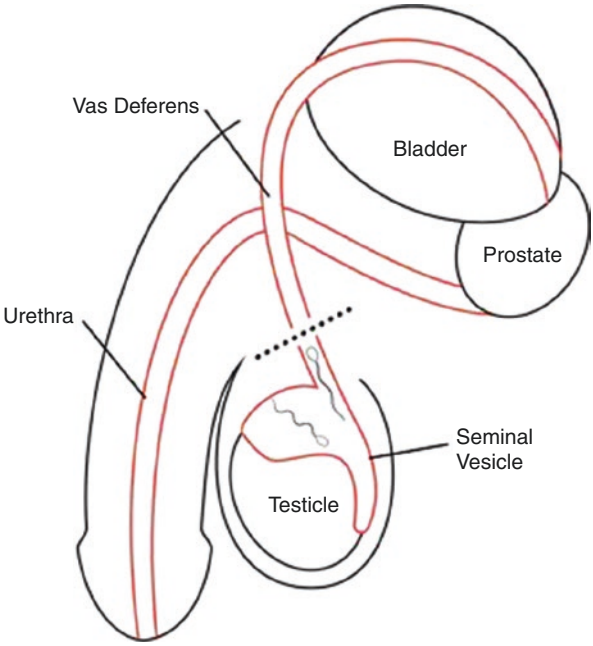

Fig. 13.1 Site of vasectomy procedure

Effectiveness and Safety

While conventional vasectomy entails an incision into the scrotum using a scalpel, modern techniques aimed at increasing the acceptability of vasectomy have been developed that avoid the need for a scalpel completely.

No-scalpel vasectomy, a minimally invasive method, has a typical use risk of pregnancy of 0.15% in the first year, which is comparable to long-acting reversible female contraception [7, 8]. In comparison, during the first year after tubal sterilization, the estimated failure rate is on average 0.5% [8]. In contrast to female tubal ligation, vasectomy does not provide immediate contraception, and so backup contraception is necessary. While the procedure itself can be performed in an office setting and on average takes about 10–15 minutes under local anesthesia, follow-up semen analysis is required to confirm azoospermia. The postvasectomy semen analysis (PVSA) should be performed 8–16 weeks after the vasectomy procedure. After one PVSA with azoospermia or rare nonmotile sperm ≤100,000 (RNMS), backup contraception is no longer necessary [3], as the risk of pregnancy is about 1 in 2000 with azoospermia [9] and similarly with RNMS [10]. A repeat vasectomy should be considered if any motile sperm persist on PVSA 6 months post-procedure, which is a rare occurrence at ≤1% [3].

In addition to efficacy, vasectomy provides a more cost-conscious and safer alternative to female permanent contraception.

A 2012 cost index cites the average cost of vasectomy as approximately $708, compared to the average cost of tubal ligation methods at $2912 [11, 12]. Some clinics even offer vasectomies out of pocket for as low as $200, while a tubal ligation may still be upward of $1000. With regard to safety, tubal ligation is 20 times more likely to have major complications, given the intra-abdominal approach; tubal ligation has 12 times the risk of procedure-related mortality than vasectomy [7, 12, 13]. Immediate postoperative complications associated with vasectomy include bleeding, hematoma formation, seminoma, epididymal or vasal pain, and infection. About 1–2% of patients experience these risks [3], though higher-volume surgeons have less complications than other clinicians [14]. Costs of bleeding and infection

each year following female and male sterilization are $62.52 vs. $0.06, respectively [11, 15]. These characteristics make vasectomy a quick, safe, effective, and cost-effective procedure that could rival the use of female sterilization among couples desiring permanent contraception.

Advantages and Disadvantages (Table 13.1)

Preoperative Counseling and Considerations

Contraceptive counseling should include the full range of reversible and permanent options and be approached with patient autonomy in mind. Vasectomy counseling should therefore include all methods of male and female contraception, so that the patient may make an informed choice. Given vasectomy is a permanent contraceptive procedure, clinicians should discuss with the patient his reproductive life goals, keeping in mind that a reversal procedure may not always be feasible or successful. Federal and state Medicaid regulations about informed consent regarding patient's age, circumstances, and time from consent to procedure should be considered and discussed.

Other factors surrounding vasectomy that should be included in counseling are:

- Need for backup contraception and follow-up PVSA to confirm occlusion in 8–16 weeks
- Need for additional STI prevention

Table 13.1 Advantages and disadvantages of vasectomy

Advantages	Disadvantages
Permanent, lifelong contraception	Requires surgery for reversal
High contraceptive efficacy	Waiting period for contraceptive effect
Safe	Surgical and anesthetic risk
Quick recovery	Need trained provider
Cost-effective	Possible out-of-pocket expense
No interruption in intercourse or decrease in sexual pleasure	Lack of STI protection
Privacy	Regret
Male contraceptive burden	

- Possibility of surgical complications including pain, bleeding, hematoma or seminoma formation, and infection (1–2%)
- Possibility of delayed recanalization leading to vasectomy failure (0.15%)
- Possibility of chronic scrotal pain or regret (1–2%)
- Need to refrain from ejaculation and strenuous physical exercise for 1 week
- May return to nonphysical work on the day after vasectomy
- Outpatient procedure under local anesthesia with or without oral sedation

Sexual Function

Some patients may worry about decreased sexual function after vasectomy as they may confuse vasectomy with castration. Patients should be reassured that vasectomy will not change their sexual identity nor affect their testosterone production. In regard to sexual function, studies show that sexual satisfaction may in fact increase, possibly due to decreased worry about pregnancy, for patients as well as their partners [16–18]. This should be discussed in preoperative counseling as patients may be hesitant to inquire about changes to sexual function.

Chronic Scrotal Pain

While a rare risk at 1–2%, chronic scrotal pain can affect one's quality of life following a vasectomy procedure [3]. Postvasectomy pain syndrome is defined as at least 3 months of chronic or intermittent scrotal content pain. In contrast, postprocedure pain usually resolves within 2–4 weeks. The etiology of postvasectomy pain syndrome is unknown, and postulations include damage to the scrotal and spermatic cord nerve structures via inflammatory effects of the immune system, back pressure effects in the obstructed vas and epididymis, vascular stasis, nerve impingement, or perineural fibrosis [19]. After a complete genital exam to rule out other causes, pharmacotherapy with nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered the first line. Other medications including tricyclic antidepressants and anticonvulsants may also be considered, followed by a series of spermatic cord neural blockades. Pelvic floor physical therapy, acupuncture, and a psychological evaluation may also be beneficial. If nonsurgical options fail, repeating the vasectomy with wide excision of the proximal and distal severed ends, microdenervation of the spermatic cord, epididymectomy, vasectomy reversal, or orchiectomy should be considered [20]. Therefore, the risk of chronic scrotal pain should be included in preoperative counseling.

Regret

Approximately 1–2% of vasectomy recipients will regret their decision [21] which is lower than women experiencing regret with tubal ligation. In fact, female partners of men who receive vasectomies have similar regret to women who have had tubal ligations, 6.1% vs. 7.0%, respectively. In addition, tubal ligation and vasectomy recipients have an increased likelihood of regret if there is substantial conflict between partners prior to the procedure [22]. The most common reason for regret was desire for more children; however, some patients may feel a problem following the vasectomy may be attributed to the procedure. Still, 80–100% of patients who underwent vasectomy would recommend it to others [3]. Therefore, preoperative counseling should include regret in efforts to obtain informed consent. However, the age of a patient, relationship status or dynamics, and number of previous children should not preclude a patient from receiving a vasectomy.

Desire for Vasectomy Reversal

While vasectomy is performed for permanent contraception and should only be pursued if irreversible contraception is desired, situations in a man's life may change prompting desire for future fertility. Assisted reproductive technology with microsurgical sperm retrieval and in vitro fertilization (IVF) is one option, while vasectomy reversal is another. Approximately 3–6% of men opt for a vasectomy reversal due to the death of a child or divorce and remarriage, change in financial situation, desire for more children within the same marriage, or in efforts to alleviate postvasectomy pain syndrome [23]. However, several factors influence the success of reversal including the time interval of obstruction between vasectomy and reversal, presence of antisperm antibodies, partner factors, history of inguinal surgery, surgeon experience, and testicular segment length [24]. Ten years of obstruction was originally thought to be the point of precipitous decline [25], but newer studies with advanced microsurgical techniques and long-term data show a gradual decline in fertility with longer obstructive intervals [24]. The overall patency rate and live birth rate of vasectomy reversal via vasovasostomy in the peer-reviewed literature are approximately 85–98% and 38–84%, respectively [26, 27]. Vasectomy reversal ranges between $5000 and $10,000, under local or general anesthesia. IVF with intracytoplasmic sperm injection (ICSI) after microsurgical sperm retrieval involves procedures for both partners, increasing costs overall. Published overall clinical pregnancy rate with ICSI for obstructive azoospermia is about 35% [28]. Given the costs of both methods can be insurmountable for some patients, as they are procedures often not covered by insurance, patients should be adequately counseled on the permanence of vasectomy procedure preoperatively. Sperm freezing and storage can also be considered preoperatively.

Antisperm Antibodies (ASA)

Men desiring future fertility after a vasectomy procedure more commonly have antisperm antibodies present compared to men in the general population [29]. However, there is no evidence of long-term adverse health outcomes in men with antisperm antibodies [30]. While pregnancy rates may be reduced by high-level antisperm antibodies in the semen after vasectomy reversal [31], the presence of antisperm antibodies should not preclude vasectomy reversal.

Health Effects

> According to the AUA vasectomy guidelines, clinicians do not need to routinely discuss prostate cancer, coronary heart disease, stroke, hypertension, dementia, or testicular cancer in pre-vasectomy counseling of patients because vasectomy is not a risk factor for these conditions.

A meta-analysis of nine cohort studies [32–39] found that the risk of prostate cancer is not greater in vasectomized versus non-vasectomized men (RR 1.08; 95% confidence interval 0.88–1.32, 3). There has also been no association found between coronary heart disease and vasectomy [40] or stroke and vasectomy [41]. Therefore, these myths should be dispelled if they arise during preoperative counseling.

Preoperative Assessment

A full medical history and male genital exam should be performed before a vasectomy procedure is attempted. While antibiotics are not routinely recommended [3], some patients, such as those with impaired healing, may benefit and the surgeon's judgment may be used. Preoperative lab assessments are also not routinely necessary [3]; however, patients with certain medical conditions may warrant more testing, such as coagulation time. On preoperative exam, special attention should be focused on patient comfort as well as identifying inguinal hernias, varicoceles, hydroceles, or cryptorchidism as these may influence whether additional procedures are necessary to identify the vas deferens and if general anesthesia is recommended. Based on the full history and exam, the surgeon may determine whether additional exams or tests and/or whether a procedure under general anesthesia may be necessary.

Vasectomy Procedure

The surgeon should have adequate training on the procedure and all necessary equipment prior to performing the procedure. The room temperature should be kept warm (68–77°F) to allow for relaxation of the scrotal muscles and skin. The patient may be asked to trim any scrotal hair in advance to about ¼ inch. The penis should be retracted cranially, and antiseptic solution, e.g., chlorhexidine or Betadine, applied to the entire scrotum and inner thighs. Sterile drapes should be placed around the surgical field allowing adequate scrotal exposure.

Anesthesia

Most vasectomies are performed under local anesthesia in physician offices with or without oral sedation. Local anesthesia is infiltrated into the skin and perivasal tissues and can also be used for a spermatic cord block. Generally, a 24- to 32-gauge needle can be used, and the smallest available should be used to minimize discomfort. Intravenous moderate sedation, deep sedation, or general anesthesia, however, may be considered in patients with concurrent medical conditions or those needing additional procedures at the time of vasectomy. Nevertheless, the risks associated with deeper anesthesia should always be weighed against its benefits.

No-needle vasectomy has been advertised to reduce pain during the procedure. Instead of a needle infiltrating local anesthetic, pneumatic pressure may be used to create a high-pressure spray of 0.1 cc into the skin and perivasal tissues. Two or three injections are delivered to each vas 2–3 mm apart, during the no-scalpel technique, and onset is within 10–20 seconds following delivery [42]. A comparative study of local infiltration anesthesia (LIA), LIA supplemented with spermatic cord block (LIA + SCB), and no-needle jet anesthesia found that pain during anesthetic administration was significantly less with LIA + SCB versus LIA alone, and there was no statistical difference between LIA + SCB and no-needle jet anesthesia. However, intraoperative pain after LIA + SCB was significantly less than after no-needle jet anesthesia [43] (Fig. 13.2).

Vas Isolation

After anesthesia is given, the first step in vasectomy procedure is vas deferens isolation. This can be performed in the conventional fashion with a larger incision, or with a minimally invasive approach, which includes no-scalpel vasectomy (NSV). One midline or two bilateral skin openings may be made. Given less pain and lower complication rates, a minimally invasive approach is the standard of care.

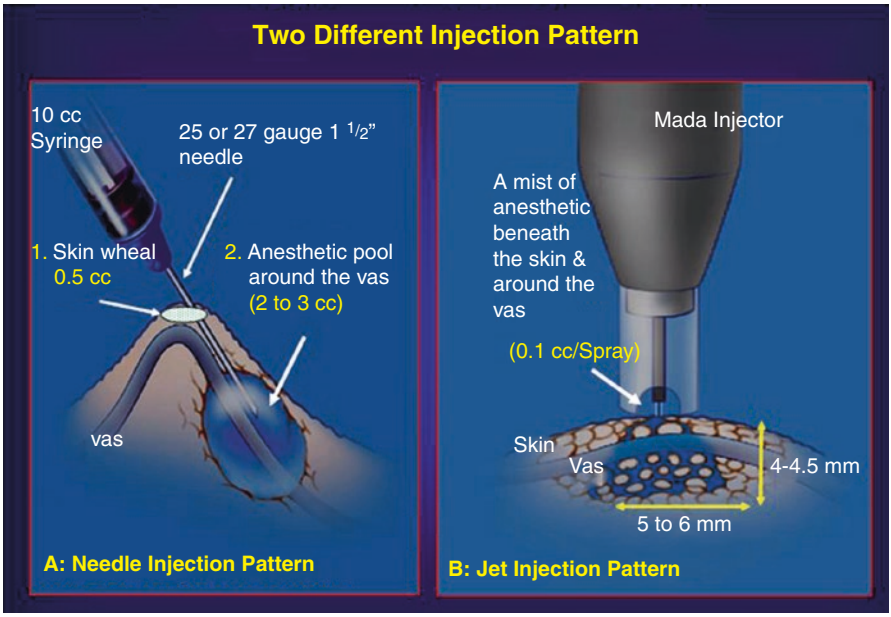

Fig. 13.2 Local infiltration anesthesia with spermatic cord block versus no-needle jet anesthesia. (**a**) Needle injection pattern. (**b**) Jet injection pattern (Source: The Journal of Urology, [42] with permission)

Conventional Vasectomy

During conventional vasectomy, skin incisions are made about 1.5–3 cm long, cutting the tissue with a scalpel. Standard surgical instruments are then used to dissect and isolate the vas deferens. After occlusion is complete, the skin incisions must be closed with suture.

Minimally Invasive Vasectomy

Alternatively, minimally invasive vasectomy involves the use of specialized instruments that allow for tissue separation to create small <1 cm openings and minimal dissection around the vas deferens. No-scalpel vasectomy was the first MIV technique described, and the specialized instruments created for this technique may be used for other MIV techniques. For example, after immobilizing the straight portion of the vas using the three-finger technique [44], the dissecting forceps can be used to dissect down to the vas before applying the ringed clamp, also referred to as a U clamp or vasectomy clamp (Fig. 13.3).

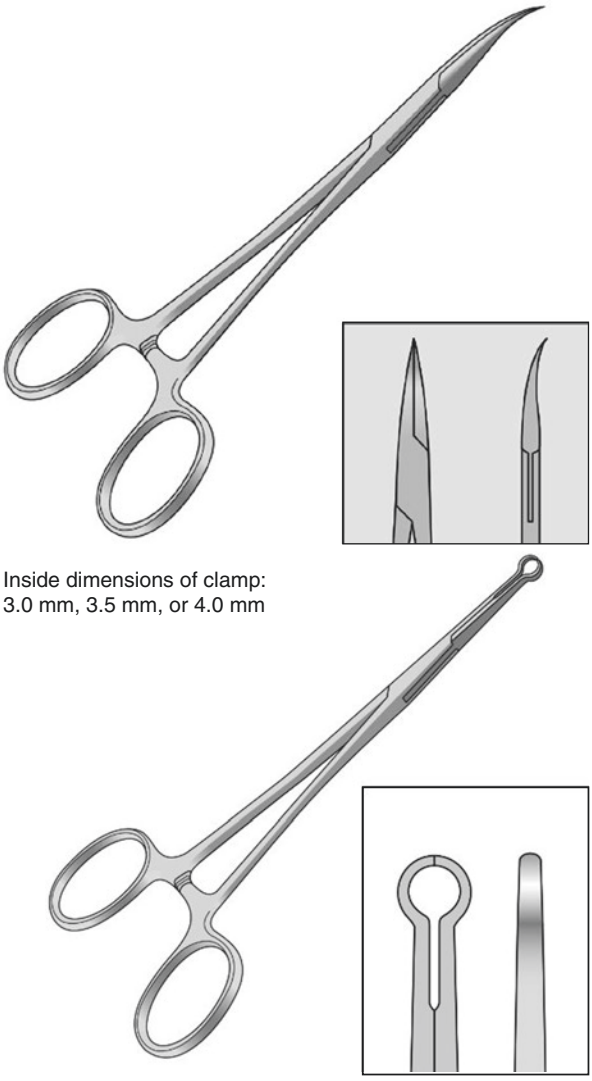

Fig. 13.3 Specialized vasectomy instruments: dissecting forceps and vasectomy or U clamp (Source: EngenderHealth, [44] with permission)

No-Scalpel Vasectomy

The no-scalpel vasectomy technique was developed in 1974 in China by Dr. Li Shunqiang to make vasectomy more acceptable to patients. A vasectomy can only be called NSV if the exact same steps are utilized. After anesthesia and localization of the vas, the ringed U clamp is used to isolate the skin, perivasal tissues, and vas deferens. The dissecting forceps are then used to dissect down to the vas and spear the vas (Fig. 13.4).

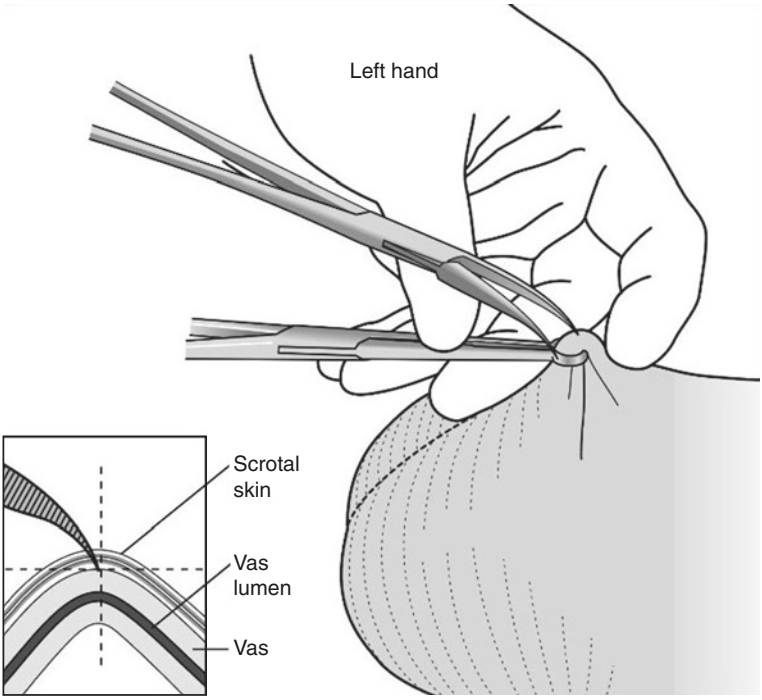

Fig. 13.4 Piercing the skin with the medial blade of the dissecting forceps. (Source: EngenderHealth, [44] with permission)

A rotating wrist movement then elevates the vas through the puncture hole as the U clamp is released and reapplied on only a partial thickness of the loop of vas. The dissecting forceps are then removed and used to puncture the vas sheath below the vas, carefully avoiding the vas artery. The forceps are then opened longitudinally to strip the vas sheath from the vas [44]. Given no-scalpel vasectomy is a surgical approach for isolating and delivering the vas, conventional methods are used for vasal occlusion.

Vas Occlusion

Surgeon experience and variations in techniques of vasal occlusion affect the failure rate of vasectomy. Therefore, the AUA Vasectomy Panel defined the acceptable rate of vas occlusion failure to be ≤1% across multiple studies conducted by different surgeons with large numbers of patients (Fig. 13.5).

Four techniques satisfied the criterion of ≤1% failure rate and, therefore, are recommended [3].

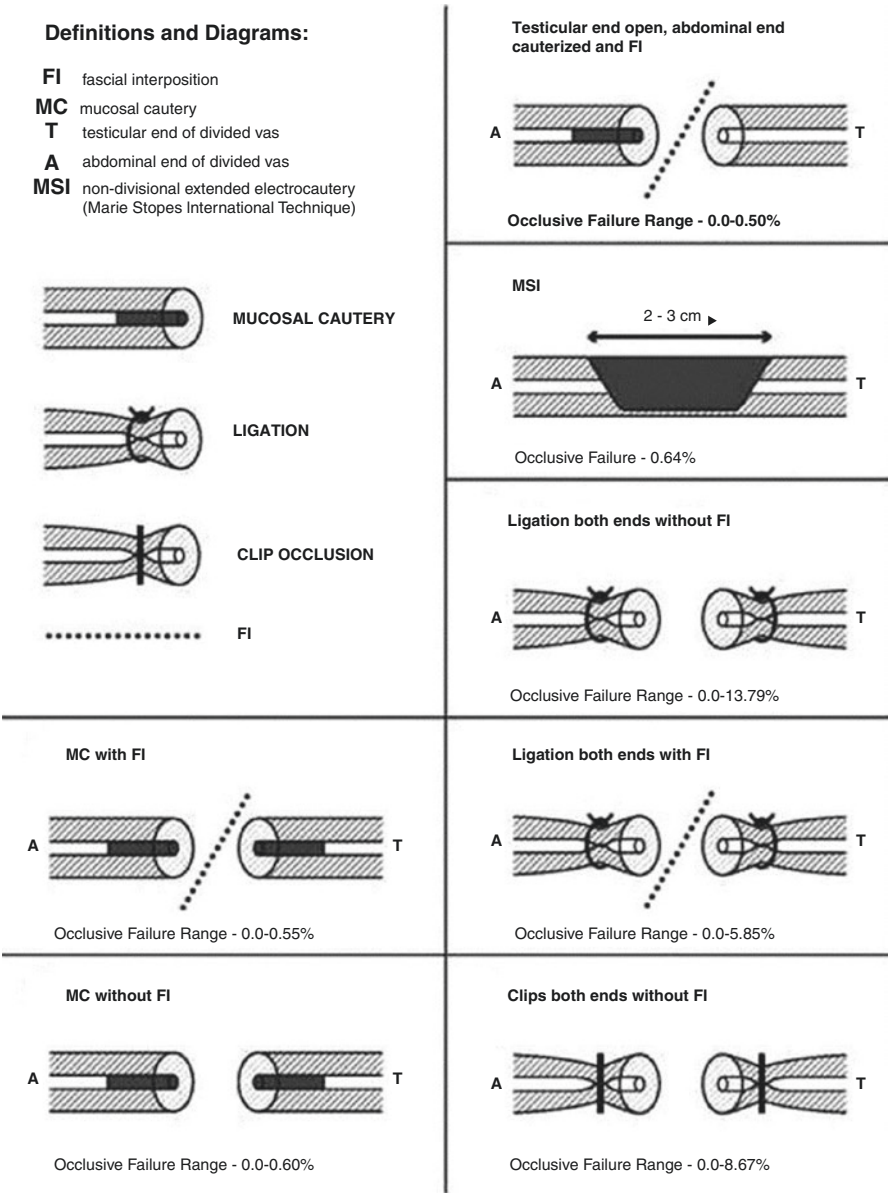

Fig. 13.5 Vasal occlusion techniques with their occlusive failure rates. (Source: American Urological Association [3], with permission)

The ends of the vas should be occluded by one of three divisional methods:

1. Mucosal cautery (MC) with fascial interposition (FI) and without ligatures or clips applied on the vas
2. MC without FI and without ligatures or clips applied on the vas
3. Open-ended vasectomy leaving the testicular end of the vas unoccluded, using MC on the abdominal end and FI; OR by the non-divisional method of extended electrocautery

While the above methods are recommended, surgeons achieving ≤1% failure rates with preferred methods are justified in their techniques. In addition, excision of a segment of the vas is not necessary, but if the surgeon prefers, 1 cm is adequate. After vasal occlusion is achieved bilaterally, skin openings <1 cm may be sutured or glued, though they do not require either (Fig. 13.6).

Complications and Follow-Up

Even though vasectomy is a safe procedure with few complications, care must be taken to avoid intraoperative complications, such as excessive bleeding, lidocaine toxicity, vasovagal reaction, and unsterile technique. Minor bleeding, hematoma formation, bruising, and pain generally improve within 1–2 weeks and can be symptomatically treated with scrotal support and mild pain medication. Edema of the scrotum will also subside and can be treated with local application of ice. While routine postoperative genital exam is not necessary, significant complications extending beyond 2 weeks should be further evaluated.

Patients should be advised that blood in ejaculations 1 week postoperatively can occur and should not raise concern. Sperm can be present in ejaculations after

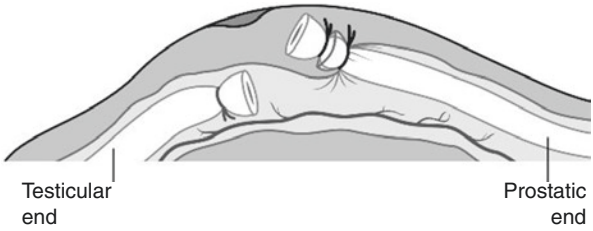

Fig. 13.6 Completed fascial interposition, with the stump of prostatic end outside the fascial sheath and the stump of the testicular end inside the fascial sheath. (Source: EngenderHealth [44], with permission)

vasectomy, and backup contraception should be used. After 8–16 weeks, depending on surgeon's preference, a postvasectomy semen analysis should be performed. Only after azoospermia or RNMS ≤100,000 is confirmed on PVSA should patients be advised that backup contraception is no longer necessary. If motile sperm are still present 6 months post-procedure, the vasectomy should be considered a failure and repeat vasectomy considered [3].

Patient Postoperative Instructions

Patients should be advised of the following postoperatively:

- Avoid activities that may rub or put pressure on the scrotum, i.e., bicycle riding, jumping, walking long distances, strenuous exercise, or heavy lifting, for at least a week.
- Wear tight-fitting underwear and/or scrotal support for at least 2 days to reduce pain and discomfort.
- After your procedure, apply cold packs to your scrotum alternating between 30 minutes on and 30 minutes off for at least 4 hours to reduce swelling, bleeding, and discomfort.
- In the absence of bothersome discomfort, you may return to nonphysical work on the day of or the day after vasectomy. You may resume physically demanding work or recreation when pain permits.
- The scrotum may appear discolored and be sore as it is healing, which can be expected. Blood may also be present in ejaculations for up to 2 months, which should not elicit concern.
- You may take NSAIDs or acetaminophen for pain as instructed.
- You may bathe 24 hours after the procedure but allow water and soap to run over the incisions and do not scrub or immerse yourself in water for at least a week. Pat the incisions dry.
- If stitches are present, they will dissolve and do not need to be removed.
- Remember to return for a postvasectomy semen analysis when instructed by your provider.
- Use backup contraception until further instructed.
- Contact your provider if you experience fever >100.4 °F, pain that is unrelieved by your pain medications, bleeding or foul-smelling discharge from incision sites, swelling twice normal scrotal size, or painful groin lymph nodes.

Role of Women's Health Providers in Vasectomy Counseling and Provision

As the primary providers of family planning services, women's health clinicians should routinely counsel couples seeking permanent contraception on vasectomy in addition to female methods. As outlined above, vasectomy is a quick, efficacious,

safe, and cost-effective method for permanent contraception. It is also an opportunity for male involvement in contraceptive responsibility [45]. Therefore, women's health providers should be knowledgeable on the procedure, as well as its risks and benefits.

For women's health providers interested in performing the procedure for their patients as well, there are a few opportunities for training. In Alaska and Washington, where there is full practice authority, nurse practitioners may provide vasectomies independently. In 2017, HB2103 passed in the Oregon legislature to allow nurse practitioners to perform vasectomies to help alleviate the Planned Parenthood vasectomy waiting list of nearly 100 men long [46]. These states where nurse practitioners perform vasectomy may allow for easier training of women's health nurse practitioners in the procedure. Additionally, family planning fellowship programs and certain residency programs are opportunities for training. A study at an OB/GYN residency program at Northwestern Memorial Hospital found that 58% of residents agreed that they would like to provide vasectomies [47]. To date, vasectomy training for OB/GYNs has been provided by programs at the University of Southern California and the University of Utah [6]. Increased demand for vasectomy training may promote collaborations with institutional urology or family medicine departments and Planned Parenthood. By being able to obtain vasectomy procedure in addition to counseling from women's health providers, couples may be able to access all their contraceptive options more readily and decrease disparities in access to this safe and efficacious permanent contraceptive method.

Conclusion

Even though vasectomy is a quicker, safer, more effective, and more cost-effective permanent contraceptive method compared to tubal ligation, the primary reasons why it is underutilized include a lack of patient and provider awareness about the procedure, frequent misconceptions about the method, relative lack of access to vasectomy, and family planning program and provider bias, with contraception still largely perceived to be a woman's responsibility [48, 49]. As women's health providers often counsel on contraception, knowledge of vasectomy and including it in discussions on permanent contraception provides a safer and more effective alternative to tubal ligation for the couple. Lastly, training in vasectomy procedure may also help patients overcome barriers in vasectomy access leading to increased utilization of this advantageous method.

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Part II
Evidence Based Practice Guidelines

Chapter 14
Choosing the Right Contraceptive

Matching Users with a Best Method: Healthy Reproductive Age, Obesity, Androgen Excess, Excess Bleeding, Adolescents, Perimenopausal, and Postpartum

Donna Shoupe

The healthcare provider should carefully evaluate each user, identify important medical issues and particular user preferences and abilities, review LARC and other contraceptive options with the patient, and most importantly help the user to select a contraceptive method that she will use safely, consistently, and correctly.

Specific Populations and Problems

Healthy Reproductive Age

Recommended: First-line choice is LARCs; also, good choices for most are COCPs, CVR, norelgest- or new levo-patch, DMPA, and POPs including the new drospirinone 24-4 only option.

The healthy reproductive-aged woman is looking for a method that is effective and easy to use with few side effects. While oral contraceptive pills along with rings and patches have traditionally been the most popular methods in the United States, the highly effective LARC methods (IUDs and implant) are gaining increased popularity [1, 2]. The number of women in the United States using a LARC method as their method of choice increased from 2.4% in 2002 to 3.7% in 2007 and then

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jumped to 8.5% in 2009 [2]. In one report done in 2012, the prevalence of LARC use among contracepting females in the United States rose to 11.6% [3]. These recent increases in LARC used (largely due to increases in use of intrauterine devices) were spread almost uniformly across various race, income, and age groups [3]. A study conducted in 2015 in a waiting room in China reported that among 381 respondents, 35.2% intended to use IUDs and 13.9% intended to use implants postabortion [4].

In addition to its high contraceptive efficacy [99%], the levonorgestrel IUD initially releasing 20 mcg/day [levo-20 IUD] and to a lesser degree the levo-17.5 IUD and the levo-14 IUD have very favorable bleeding pattern and have become important therapeutic tools for use in reproductive-aged women with bleeding problems [5]. While all of these hormonal IUDs are generally associated with lighter periods, after insertion of the levo-20 IUD, 20% will have no bleeding starting during the first year, compared with 12% in levo-17.5 IUD users and 6% in the levo-14 IUD users.

If used correctly, the modern contraceptives are effective or very effective in preventing pregnancy. Only 5% of all unintended pregnancies in the United States occur in two-thirds of women who use their contraceptive method correctly and consistently. The 18% of women who do not use their contraceptive method consistently account for 41% of the unintended pregnancies in the United States [2].

Clearly the goal of the practitioner is to educate about all methods, promote use of the LARC methods due to their high efficacy, address concerns, review contraindications, and ultimately select a method that the *patient will use correctly*, *consistently*, *and safely.*

Good Options

1. General reproductive-aged women seeking contraceptive protection should first consider the LARC methods (IUDs or subdermal implants) due to their high contraceptive effectiveness and broad safety profile.
2. Those who are not in stable relationships should also consider adding a barrier method for protection from STDs.
3. Most healthy reproductive-aged women are good candidates for combined hormonal contraceptive methods (CHCMs) including COCPs (combination oral contraceptive pills), CVRs (contraceptive vaginal rings), and contraceptive patchs (norelgest-patch or new levo-patch for women < 30 kg/m^2), although screening for migraine headaches, smoking, hypertension, and long-standing or severe obesity along with the other danger flags should be routine. One of the CVRs, contraceptive implants, or patchs may be better options for those CHCM candidates who have difficulty complying with the necessity of daily compliance.
4. There are two progestin-only pills on the market, one with norethindrone and a new one (Slynd) containing drospirenone in a 24-4 regimen. Slynd is taken daily [anytime] and is associated with good bleeding control.

Selecting the method that the patient is most likely to use correctly and consistently is the goal. Fortunately, cost issue for many women is less of an issue since the affordable healthcare plan mandated that contraceptive methods be covered by health insurance plans.

Counseling General Reproductive-Aged User: Concerns – Cancer Risk

The primary health concern for many reproductive-aged women seeking contraceptive protection is cancer risk, particularly the risk of breast cancer. The studies reporting the risk of breast cancer with the use of various contraceptives have had inconsistent findings. Many studies show no increase in breast cancer risk. Generally, the studies that have reported increased risks of cancer have reported that these risks have been very small and reversible after discontinuation of the method. An analysis of breast cancer risk and OC use among women 35–60 years of age reported no increased risk associated with current or past OC use [6]. However, a worldwide analysis of all reproductive-aged women found a slightly increased risk among current or recent OC users. This increased risk disappeared after 10 years of discontinuation, and the cancer incidence in users was identical to nonusers after age 65 [7]. Similarly, the use of DMPA is reported not to increase the overall breast cancer risk in some studies, while other studies show a small transient increase during use [8, 9].

Coupled with a discussion of breast cancer risk should be a discussion of the *protective effects* of COCs and other contraceptive methods on other types of cancer. See Table 14.1.

Table 14.1 Reported reductions in cancer risks with the use of specific contraceptive methods compared with nonusers

	Use duration	Risk reduction
Endometrial cancer		
Combination OCs [10, 11]	1 year	40%
	12 years	72%
	20 years after stopping	50%
DMPA [12]	Ever use	79% (protection persists ≥8 years after stopping)
Progestin IUDs [13–16]	Limited data	40–60%
Ovarian cancer		
Combination OCs [17–19]	3–6 months	40%
	>5 years	50% (protection persists ≥30 years after stopping)
Colorectal cancer		
Combination OCs [20]	Ever use	16–18%
	96 months	40%

OC oral contraceptive, *DMPA* depot medroxyprogesterone acetate, *IUD* intrauterine device

The reported effect of various contraceptive methods in reducing the risk of endometrial, ovarian, and colorectal cancer is shown in Table 14.1. Other common concerns are discussed below under concerns of the perimenopausal woman.

Obesity

Recommended: LARC methods (LNG-IUD and LNG-implant, followed by Cu IUD) are particularly good first-line contraceptive choices for many obese reproductive-aged women. CHCMs may also be a safe choice for selected women in this population.

In 2012, 32% of reproductive women were classified as obese. By 2015–2016, the prevalence of obesity in the United States was 39.8% affecting over 93 million adults. The healthy normal weight is a BMI of 18.5–24.9 kg/m^2. Benign obesity is defined as a BMI >30 kg/m^2 with only zero to one metabolic syndrome component. At-risk unhealthy obesity is defined as a BMI >30 kg/m^2 with two or more metabolic syndrome components as listed below:

1. Triglycerides ≥150 mg/dl
2. HDL <50 mg/dl and/or use of lipid-lowering medication
3. Glucose ≥100 mg/dl
4. Hypertensive and/or use of antihypertensive medication

Besides multiple long-term health consequences, obesity also increases the risk of venous thromboembolism. This risk is significantly further magnified in this population for those taking combination oral contraceptive pills (Table 14.2).

Good Options

1. CDC classifies the IUDs, ETO-implant, DMPA, and POP (including the new drospirenone option) as category 1 (no restriction).
2. Combined hormonal contraceptive methods (CHCMs) are classified as category 2 (advantages generally outweigh risks) for women with obesity. However, consideration of older age, BMI >35, or the presence of metabolic syndrome components (listed above) may indicate significant increased risk for combination products.

Table 14.2 Risk of venous thromboembolism in obese women with the use of COCPs [21]

BMI	Not on COCs	On COCs
<25	1	4.15
25–30	2.52	11.63
>30	4.15	23.78

3. MEC category after restrictive surgery for obesity is 1 for LARCs, DMPA, norelgestpatch, CVRs, POPs, and emergency contraceptives.
4. MEC category after malabsorptive surgery is 1 for LARCs, DMPA, norelgestpatch, and CVR but 3 for COCPs, POP, and emergency contraceptives. In women with BMI >35 kg/m^2, the use of COCPs, norelgestpatch (specifically less effective in women over 198 pounds), and emergency contraceptive pills is associated with an increased failure rate [22].

However, the use of any hormonal contraceptive is more effective at preventing pregnancy than using no method, and obese women need a candid discussion on the risks and benefits of all methods.

While providers would like to use as low-dose COCP as possible to keep the risk of VTE as low as possible, there is evidence that the lower-dose COCPs are less effective in obese women and may have higher breakthrough bleeding rates. Using a low-dose pill with a shorter pill-free window may improve efficacy and decrease breakthrough bleeding rates [23].

Studies have reported altered hormone metabolism and increased failure rates in obese patients using COCPs, the norelgestpatch, or emergency contraceptive pills. Several studies in obese women (BMI >30) using the ETO-implant reported lower etonogestrel (ENG) levels compared to normal weight women suggesting a need to replace the implant sooner than 3 years.

There is also evidence that drug–drug interactions are of particular concern for obese women as they are possibly "closer to the edge" of contraceptive effectiveness. Data indicates particular drugs of concern including efavirenz, antibiotics, antidepressant medications, and ADHD medication.

It is important to keep in mind that as long as safety risks are considered [risks associated with pregnancy compared to risk on method], the use of any contraceptive is better than none.

Acne or Hirsutism: Androgen Excess

Recommendations: LARCs plus spironolactone, CHCMs containing drospirenone, new drosperinone only pill, CHCMs containing desogestrel, or CHCMs not-containing drospirenone or desogestrel with spironolactone

Hirsutism is a common clinical problem affecting 5–10% of women. Normal patterns of hair distribution are often determined by racial background. Generally, whites tend to have more facial hair growth than do blacks and Asians. White women with Mediterranean background tend to have more facial hair growth compared to those of Nordic countries. Hirsutism is the presence of terminal (dark and

thicker than vellus hairs) hairs in a male-like distribution. Oral contraceptives are generally first-line recommendation for the majority of women with particular emphasis on drospirenone- or desogestrel-containing OCPs.

Causes of Hirsutism

Hirsutism is usually the result of testosterone stimulation of fine, pale, faintly visible hair follicles (vellus hair) causing them to thicken and darken becoming terminal hair. Free-testosterone (not bound to SHBG or albumin) is converted to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase that is present in the outer root sheath of hair follicles. DHT causes the vellus hair to thicken and darken. About 20% of hirsute patients present with idiopathic hirsutism with normal levels of androgens but increased sensitivity of hair follicles to circulating androgens (usually testosterone).

Hirsutism may result from high testosterone levels (usually from the ovary [often PCO or hyperthecosis)]. Less commonly hirsutism is the result of overproduction of androgens in the adrenal gland. Overproduction of adrenal androgens may be due to an adrenal tumor, congenital adrenal hyperplasia (CAH – due to a congenital enzyme deficiency most commonly a 21-hydroxylase deficiency, *diagnosed with high 17-OH progesterone measurement*), or Cushing's disease. Idiopathic hirsutism results from overstimulation of hair follicles in the presence of normal testosterone levels. A rare cause of hirsutism is hyperandrogenic-insulin-resistance-acanthosis nigricans syndrome.

Bodybuilding steroids, certain progestins, other circulating androgens, and many types of medications (cyclosporin, danazol, anabolic steroids, metoclopramide, methyldopa, phenothiazine, reserpine, phenytoin, minoxidil, and penicillamine) can also cause hirsutism.

Hypertrichosis, excessive hair growth that does not fit the pattern of androgen pattern growth (not on upper lip, sideburn area, chin, lower abdomen, or around nipples), may be due to thyroid problems, long-term meds (as listed above), or anorexia nervosa. Measurement of testosterone (sometimes DHEAS) is indicated with moderate to severe or progressive hirsutism. Levels of testosterone above 150–200 ng/ml should be followed by ultrasound of the ovaries, while levels of DHEAS above 700 ng/dL (or very high testosterone and no ovarian lesion) should be followed by MRI of adrenal gland.

Evaluation and Workup: Hirsutism

A detailed history of onset and progression of symptoms, signs of virilization, weight gain, diabetes, and drug history should be taken. If drug is the cause, withdrawal of the drug may be indicated. In the physical exam, palpation for presence of pelvic or abdominal mass, thyroid abnormalities, and presence of hirsutism or acne are key features.

The Ferriman and Gallwey Scale was developed to clinically quantify the severity of hirsutism. There are nine sites: upper lip, chin, chest, arms, upper back, lower back, upper abdomen, lower abdomen, and thighs. Each site is scored on a scale from 0 to 4. A score of >8 is consistent with hirsutism. This scale is subjective and not used by all.

Initial Testing

1. If testosterone is over 150–200 ng/ml, a pelvic ultrasound is indicated.
2. In cases with severe, progressive hirsutism or when testosterone is not elevated, a DHEAS may also be indicated. A DHEAS >700 μg/dl requires MRI of adrenal gland.

More thorough workup for hirsutism is indicated when there are additional problems including irregular or absent cycles (thyroid testing) and galactorrhea (prolactin, TSH), or see below for rapid-onset hirsutism, uncontrollable acne or hirsutism, or virilization including deepening voice, receding scalp, thinning hair, decreased breast size, increased size of clitoris, or increased muscle mass (17-OH progesterone, pelvic u/s).

Workup: check for darkened skin patches in axilla, vulva, and neck areas, obesity or weight gain, order HbA1c, for weight gain, hypertension, high blood sugar, prepubertal hirsutism, difficult-to-control acne or hirsutism, muscle loss, and central obesity order 24-hour urinary free cortisol.

Advanced Testing

3. In selected cases, evaluation for CAH is indicated. An elevated 17-OH progesterone indicates CAH. It is best done between 7 and 9 am during the follicular phase of menstrual cycle. The diagnosis of adult onset adrenal hyperplasia is made if it is elevated. Generally treatment is with low dose dexamethasone. A 11-deoxycorticosterone should be ordered to rule out the salt-losing type of adrenal hyperplasia.
4. A 24-hour urine free cortisol is measured in women with (muscle loss, thinning skin, purple or pink stretch marks, buffalo hump, hypertension, central obesity) signs of Cushing's syndrome.
5. TSH, prolactin, pelvic ultrasound, and MRI of adrenal gland are considered in selected patients (as above).

Treatment Options: Hirsutism and Acne

Diet and exercise is advised in women with PCO and weight loss in all overweight women. While local plucking, shaving, waxing, depilatory creams, laser treatments, and electrolysis are helpful in removing the current abnormal dark hairs, *long-term treatment to prevent further recruitment of new coarse dark hairs is a good option.*

Removal of an ovarian or adrenal tumor if present, stopping selected medications, and weight loss (due to conversion of sex hormones to androgens in fat tissue) are advised.

In women with hirsutism, these are good treatment options.

1. Oral contraceptive pills (OCPs) have been a long-standing first-line long-term preventative and treatment option for hirsutism. The multiple actions of OCPs in reducing hirsutism and acne are discussed below. The new progestin-only pill with drosperinone is a good treatment option.

   Products containing the antiandrogen receptor blocker *drospirenone* (Yaz, Yasmin, Gianvi, Jasmiel, Loryna, Nikki, Ocella, Syeda, Vestura, Azrah, Lo-Zumandimine, and Zumandimine, now Slynd) are highly effective in decreasing acne (within a few weeks) and other androgenic problems (within a few months). Other products with the newer, low androgenic progestins (desogestrel and norgestimate) avoid the small pro-androgenic activity of the older progestins and are also good options.

   All combination contraceptive products (COCs) have multiple suppressive antiandrogenic actions and are usually associated with reductions in androgenic clinical complaints. These antiandrogenic actions include a direct antiandrogen action in the skin on reducing sebum production (good for reducing acne), a suppression of gonadotropin stimulation of the ovary, suppression of adrenal androgen (DHEA(S)) production, and a stimulatory effect on SHBG production that binds up and deactivates circulating endogenous androgens. OCPs with drospirenone including the new progestin only pill with drospirenone have the additional suppressive action of drospirenone on androgen receptors in the hair follicles and fat glands.
2. The use of a LARC method plus spironolactone (initial dose 100 mg daily) is also a first-line recommendation.

   Spironolactone, an oral androgen receptor blocker, is also an effective option for women who do not prefer to take OCPs or those who do not need contraception. Spironolactone competes with DHT for binding to the androgen receptor (anti-DHT action) and competes with androgens for binding to SHBG. Spironolactone has a variable progestational action and reduces production of ovarian androgen. Spironolactone should not be used with drospirenone-containing OCPs or POP due to potential hyperkalemia.

   Cyproterone acetate has strong progestogenic and antiandrogen properties and is available in Europe alone or in a specific COCP.
3. The treatment for adrenal suppression in women with high DHEA-S is low bedtime dose of dexamethasone (starting dose 0.5 mg daily).

Local skin care products and antibiotics are commonly prescribed for acne problems. A cream used for reducing facial hair growth is eflornithine hydrochloride (Vaniqa) that is available by prescription only. Eflornithine inhibits an enzyme involved in keratin synthesis in the hair follicle under the skin which slows hair growth. It is applied twice daily, and improvements can be seen as early as 4–8 weeks.

Bleeding Problems

First-line recommendations include the hormonal LARC methods or CHCM, DMPA, or new drospirenone POP.

There have been dramatic improvements in the ability of many contraceptive

The choice of medical therapy for treating patients for menorrhagia or irregular bleeding requires consideration of a multitude of factors including acuteness and severity of bleeding, coexisting medical problems, patient's age, family history, future fertility plans, patient compliance, and adverse side effect profile and cost of treatments.

options to control monthly bleeding patterns and decrease overall bleeding and cramping. For women who decline contraceptive options, other treatments are available. For ovulatory menorrhagia, nonsteroidal anti-inflammatory drugs (NSAIDs) are a first-line treatment. NSAIDs reduce prostaglandin levels by inhibiting cyclooxygenase and can reduce bleeding by 20–46% [23]. Other noncontraceptive choices include tranexamic acid and thermal balloon ablation.

The average amount of blood loss during a period is 30–40 ml. Menorrhagia is a monthly loss >60 ml in each cycle or periods lasting more than 7–8 days. Clinical signs of menorrhagia include:

1. Heavy bleeding through clothes or bedding
2. Need to use tampons and towels together
3. Bleeding or "flooding" not contained within a pad/tampon, especially when wearing the largest size
4. Change a pad/tampon every hour or less
5. Changing a pad overnight
6. Clots greater than a 50 cent piece in size
7. Bleeding for more than 7–8 days

Further testing and treatment of abnormal bleeding may include endometrial biopsy, pelvic ultrasound, hydrosonogram if intrauterine polyp or myoma is suspected, CBC if heavy or long-standing bleeding, clotting parameters especially in young patients, and hysteroscopic removal of intrauterine polyp or myoma.

Contraceptive Treatment Options

1. A popular method for decreasing bleeding problems in women seeking contraceptive protection is one of the levo-20 IUDs and also the levo-17.5 and levo-14 IUDs.

The levo-20 IUD reduces menstrual blood loss by as much as 97% [23, 24]. Multiple studies document the high success rate of the levo-20 IUD in controlling abnormal bleeding and reported as good as or better than thermal balloon

ablation, tranexamic acid, mefenamic acid, combined estrogen–progestogen pills, or progesterone alone pills [25–27].

In one study, persistence of menorrhagia within 1 year of use of the levonorgestrel IUD in women with myomas under 2.5 cm was 14%, and there are 29% failure rate with myomas 2.5–5 cm in size and 25% failure rate with those at least 5 cm in size [27].

2. OCPs are also a first-line option for women with bleeding problems seeking contraception. In a Cochrane Review, the combined oral contraceptive pill over six months reduces heavy menstrual bleeding from 12% to 77%. Limited evidence suggests that the COCPs and CVR have similar effects and that the COCPs are less effective than the LNG IUS [28].

   Dienogest/estradiol valerate (Natazia) was the first oral contraceptive approved by the FDA (March 2012) for heavy menstrual bleeding. Many of the newer oral combination pills (COCs) have been specifically designed to decrease overall monthly blood loss. A reduction in the daily estrogen dose in the COC pill, a balance of the progestin-to-estrogen ratio in favor of more progestin activity, and a change in the traditional 21-7 pill protocol have all been instrumental in decreasing blood loss. The 24-4 regimen was designed to allow for a monthly bleeding episode but not to allow the ovary to gear up estrogen production (as seen with the 7-day pill-free window for the traditional cycle) during the short 4-day window of pill-free days.

For women under the age of 25–26, the use of the traditional low-dose pills may result in breakthrough bleeding. Switching to 24-4 regimen pills (especially the ethinyl estradiol plus norethindrone acetate pill which has a high progestin to estradiol content) may have better bleeding control while decreasing monthly bleeding days and blood loss. The use of COCPs with extended cycles is also an option used to decrease overall bleeding episodes and unscheduled bleeding.

3. Other progestin therapy options are commonly used to downregulate the endometrium and significantly reduce menstrual blood flow. The use of DMPA is a good option for bleeding control as around 50% of users have amenorrhea after 1 year of use and 80% have amenorrhea after 2 years of use. For immediately stopping bothersome or acute bleeding, oral medroxyprogesterone acetate can be given 10-mg MPA, two tablets by mouth three times a day for 7 days and then two tablets by mouth once a day for an additional 21 days [29].

   In a prospective trial, 150-mg DMPA IM and medroxyprogesterone acetate 20 mg given every 8 hours for 3 days were effective in stopping bleeding within 2–5 days. Side effects were infrequent and patient satisfaction was high [30].

   Following cessation of bleeding, either levo-IUD or selected COCPs can be initiated.

4. POPs or other forms of progesterone (medroxyprogesterone acetate, norethindrone, drosperinone) can reduce blood loss by 30% [31]. The new drospirenone POP is used in a 24-4 regimen and is designed to control monthly bleeding episodes.
5. ETO-implant reduces blood loss in most women, but a certain percentage do not have decreased bleeding, and some may have increased bleeding.

Adolescents

Recommended first-line treatments are LARC methods or CHCM (COCPs, CVRs, patch) or POPs [particularly new drosperinone only pill]; addition of condoms for all methods is generally recommended.

The high rates of adolescent pregnancy in the United States are associated with high costs of public assistance, lower educational attainment, reduced earning potential, and high healthcare costs [32]. The CHOICE Project was a large prospective study designed to promote the use of LARC methods in teenage girls (ages 15–19) (and older women) in the St. Louis region. Once financial barriers were erased and education regarding LARC methods was done, two-thirds of all participants including the teenagers chose LARC methods. Education and promotion of no-cost LARC methods resulted in almost a fivefold drop in teen pregnancy, birth, and abortion rates [1, 32, 33].

> Although delaying sexual activity is the goal until responsible sexual, contraceptive, and protective behaviors for prevention of sexually transmitted infections are established, access to contraceptives, particularly LARC methods, along with STD counseling and testing is important part of adolescent healthcare.

In 2004, the Department of Health and Human Services estimated that about 47% of female and 46% of male teenagers had had sexual intercourse at least once [34]. Sexually active teenagers report that they use a contraceptive method only 75–90% of the time. Among the developed countries, the United States continues to have one of the highest adolescent pregnancy rates (70 per 1000 females 15–19). In 2009, the US birth rate in 15- to 19-year-olds was 39.1 births per 1000 females [35]. Unfortunately, teenage pregnancy is associated with high rates of welfare dependency, poverty, lack of education, and inadequate workforce training. It is also of serious concern that of the 18.9 million new cases of STIs each year in the United States, 9.1 million occur in adolescents and young adults [35]. Long-term problems associated with early sexual activity include pelvic inflammatory disease, infertility, cervical dysplasia, emotional disturbances, and criminal prosecution (Table 14.3) [36–39].

Table 14.3 Statistics on risk of STIs and HIV in young people

Of all STIs occurring each year, 50% are in young people aged 15–24 [36]
HPV is the highest STI incidence in ages 15–24 with 4.6 million new cases per year
In one study of inner city sexually active teenagers, 90% had HPV on the cervix [37]
The highest risk for cervical cancer is among those who are sexually active during adolescence and have multiple sexual partners [38]
About 25% of newly diagnosed HIV cases are in young people under age 22 years [39]

STI sexually transmitted infection

Table 14.4 Adolescent counseling

Abstinence information
Benefits of delaying (pregnancy risk, STIs, emotional issues)
Negotiation and refusal skills
Address peer pressure
Realistic expectations on condoms and other contraceptives
Limits on contraceptive effectiveness
Limits on STI protection
Accurate contraceptive information
Options and proper use
Emphasis that contraceptive and STI protection is most reliable when method is used consistently and correctly

STI sexually transmitted infection

Counseling the Teenager

In an ideal case, the healthcare provider can counsel adolescents before their sexual debut and convey to them the associated personal, social, economic, and health consequences they should consider (Table 14.4). Delaying sexual activity is clearly the goal until responsible sexual, contraceptive, and sexually transmitted infection (STI) protective behaviors are developed [40]. Multiple studies demonstrate the value and need for parental guidance as well as counseling and educational support from appropriate outside sources.

- A national research study conducted in 1468 teenagers addressed several aspects of contraceptive use among teenagers and identified some important trends [41]. In both females and males, the odds of consistent use of a contraceptive method increased with the duration of a relationship. Discussion of contraceptive use with a partner before a sexual experience was associated with a higher and more consistent use of a method. Increased number of dates before sexual activity resulted in higher contraceptive use.
- Public Opinion on Sex Education in US Schools from the *Archives of Pediatrics and Adolescent Medicine* reports the following: "Approximately 82% of respondents indicated support for programs that teach students about both abstinence and other methods of preventing pregnancy and sexually transmitted diseases" [42].

Appropriate adolescent counseling includes an emphasis on the benefits of abstaining or delaying sexual activity, the fact that no contraceptive ensures absolute protection, and information regarding potential negative consequences of unprotected sexual contact. Providing accurate, pertinent information regarding the limits of contraceptive and STI protection from currently available methods is important. Although condoms offer the best protection, no method offers complete protection from pregnancy or STI transmission. Abstinence is the only sure way to be protected. The next best option is consistent and proper use of a contraceptive method.

Adolescents, especially those choosing to begin or to continue engaging in sexual activity, should be given up-to-date information regarding LARC methods and other contraceptive choices with an emphasis on what methods are best at preventing pregnancy and best at preventing STIs [43, 44]. Many adolescents resist contraceptive or condom use for a variety of reasons, including a denial that they could become pregnant, fear or embarrassment to ask for contraceptives, lack of access, concerns about cost, fear of partner rejection, worry about parental discovery, ignorance, desire to have a child, or lack of planning. Selecting the best contraceptive method for a teen includes an assessment of psychosocial and physical development, motivation, level of understanding, financial ability, and bleeding issues or c/o dysmenorrhea. To improve compliance, delaying the pelvic exam (but not the contraceptive) in an adolescent patient is often appropriate especially in view of the recommendation that Pap smear is now not recommended until age 21.

Choosing the Correct Contraceptive Method

When choosing the type of birth control, the following factors are important to consider:

- Does the patient know about LARC methods of contraception?
- Will the patient be able to easily obtain the method?
- Does the teen have any medical contraindications to the chosen method?
- Is the teen informed on how to use and motivated to properly and consistently use the chosen method?
- Does the teen understand the side effects associated with the method?
- Is the level of protection against pregnancy appropriate for the teen?
- Does the method address the teen's risk of STI exposure?

According to the CDC/NCHS National Survey of Family Growth 2006–2008, most sexually active teens use a contraceptive method at some time. Ever use of condoms in sexually experienced females 15–19 years of age in 2006–2008 was 95%, pill 55%, withdrawal 58%, injectable 17%, and calendar method 17%.

Although the pregnancy rate in teenagers has been on a downward trend since its peak in 1990, it remains high: 40–60/1000 adolescents. Adolescents are eligible for all methods of contraception, and dual protection should be encouraged. Since 2009, ACOG has recommended "encourage implants and IUDs for all appropriate candidates, including nulliparous women and adolescents."

Good Options

1. The ETO-implant (Nexplanon) is an ideal method for adolescents. The insertion is easy, the bleeding pattern often improves, there are no user-required actions, and the excellent contraceptive protection lasts for 3 years [32]. Progestin-only methods are associated with a change in bleeding patterns, and the potential user should be counseled accordingly. The package insert for ETO-implant reports bleeding patterns overall in users is infrequent in 33.6%, amenorrhea in 22.2%, prolonged in 17.7%, and frequent in 6.7%.
2. The intrauterine device (IUD) can be considered as a first-line choice for adolescents [32]. Many adolescents have not had a pelvic exam, and placement of an IUD may require special counseling and technique. The smaller 14 levo-IUD and the 17.5 levo-IUD have advantages that they are smaller, have lower "hormone release," and were designed for young, nulliparous women.

   WHO recommendations:

   - From menarche to younger than 20 years old, there is concern about the risk of STIs and the increased risk of expulsion owing to nulliparity; however, the benefits of either the copper IUD or levonorgestrel intrauterine system (LNG-IUS) generally outweigh the risks.
   - Pain of insertion may be decreased with the use of pre-insertion ibuprofen orally plus the use of a paracervical nerve block just prior to the IUD insertion.

> *10-ml 1% lidocaine used as paracervical injection for IUD insertion in adolescents and young women significantly reduced the patient-reported pain during the insertion 41.*

3. *Male and Female Condom*

> Counseling for most teenagers should include the short- and long-term risks associated with STIs and a realistic assessment of prevention strategies.

Most sexually active teenagers are at risk for STI exposure. A male or female condom can be used alone or used in conjunction with another contraceptive method. If

used correctly and consistently, male (and probably female) condoms substantially reduce the risk of HIV transmission [45, 46]. Condoms are not 100% effective, but in 1986, the US Surgeon General's report advised the use of latex condoms to prevent the spread of AIDS. Currently, the CDC recommends that "consistent and correct use of the male latex condoms can reduce (though not eliminate) the risk of STD transmissions" [47].

4. *Options: Oral Contraceptives, Patch, or Ring*

> Barriers to adolescents' access to the full range of contraceptive methods should be recognized and removed when possible. Assurances of confidentiality, avoidance of a pelvic examination, discussion of cost issues, and accurate information on side effects, particularly weight gain, are important goals.

The use of urine for STD testing can replace cervical specimens so as to avoid a pelvic exam in selected adolescents. While the use of LARC methods is the first-line recommendation, oral contraceptives remain a good option for motivated and responsible adolescent girls. The weekly contraceptive patch (particularly when new low-dose patch is available) has the advantage of non-daily requirement, and adding a condom for STI protection may be appropriate and highly beneficial. Teens like the bleeding control and decline in menstrual cramps and acne that COCPs provide. There is no evidence of an adverse effect on growth or maturation of the hypothalamic–pituitary axis by taking hormonal contraceptives when started in healthy, menstruating adolescents. As long as a girl has had at least three regular, presumably ovulatory menstrual cycles, it is generally safe to prescribe COCPs, CVRs, or norelgest-patches.

In choosing the correct contraceptive method for a sexually active, healthy adolescent, the clinician should be particularly concerned about the ability of the teen to use the method correctly. COCPs are relatively easy to use, regulate and reduce menstrual bleeding, and reduce menstrual cramps and acne. These are good reasons for teenagers to keep taking OCs. The CVRs and norelgest- or lower dose LVG-patch offer these same benefits, but they have the added benefit of a once-a-month or once-a-week dosing. In a study in adolescents, consistent and proper use of the ETO-patch was significantly better than the inconsistent adherence seen with COCP use [48]. Side effects of breast tenderness, nausea, and headache may occur. These side effects and safety may be improved with the use of a new lower-dose patch now undergoing FDA evaluation.

The following suggestions may improve OC compliance and effectiveness among adolescents:

- Cue use of method to a daily activity, e.g., near sink in morning.
- Explain protocol for missed dose.
  - Establish liberal prescription renewal.
  - Advise regarding necessary yearly follow-up visits.

- Emphasize other benefits, including less acne, less hirsutism, less dysmenorrhea, less bleeding, limited protection from upper tract tubal infections, and more regular menses.
- Risks of the method should be put into perspective while also emphasizing the safety and effectiveness of the method.
  - A nonsmoker aged 15–19 years using OCs has a method-related mortality rate of 0.3 per 100,000 women per year. Compare this with a mortality rate for motor vehicle accidents of 19.6 per 100,000 in the general population or with 7 per 100,000 pregnancy-related deaths in this age group. The noncontraceptive benefits should be addressed (Table 14.1).
- Prepare the adolescent for breakthrough spotting or bleeding that may occur during the first few months of use. Advise "not to stop method" until they have visited a healthcare provider.
- Discuss that emergency contraception (single dose Plan B) is on shelf at retailers, coupons available online. Plan B should be taken as soon as possible after unprotected intercourse and no later than 72 hours afterward.
  - Ella is prescription pill that should be taken within 5 days of unprotected sex or failed birth control method (should wait for 5 days to start using hormonal birth control after taken).
- Inform the user of what to do with missed pill (with one missed pill, take two on the next day and then take rest of pack as normal; if two or more pills are missed, take last missed pill right away and take rest of pack as normal, back up, or practice abstinence for 7 days. If pills are missed in the first week, emergency contraception should be considered if the patient had unprotected sex in the pill-free interval or first week of pill packet.
- Discuss weight gain. Although some cyclic fluctuations may occur, OCPs and norelgest-patches are generally not associated with a weight gain of more than 0.5 lb.

5. *Progestin-only methods: Depo-Provera (DMPA) and Depo-subQ Provera 104™ or new drospirenone POP.*

According to the US Department of Health and Human Services' *Health, United States, 2004: With Chartbook on Trends in the Health of Americans* report, nearly 10% of adolescent girls aged 15–19 chose depot medroxyprogesterone acetate (DMPA) as their method of contraception, as compared with only 3% in the overall contraceptive market (ages 15–44). In all age groups, the use of DMPA should be accompanied with promotion of adequate daily calcium and exercise. Depo-subQ Provera 104 (Depo-subQ) is a lower dose than DMPA and is injected subcutaneously rather than intramuscularly. It is also approved for treatment of pelvic pain associated with endometriosis.

DMPA and Depo-subQ are highly effective methods that may be particularly good in teens that do not want to take a pill every day. Other good candidates include teens that have become pregnant on OCs, those that forget to take their pills every day, or those who have discontinued use of OCs because of side effects. DMPA and

Depo-subQ are administered every 3 months and may be more cost-effective compared with other methods. The irregular bleeding, weight gain, or amenorrhea [49] that may occur during DMPA may lead to discontinuation. Adequate counseling regarding the early bleeding changes and later amenorrhea, and potentially a better side effect profile with the use of the lower-dose Depo-subQ, may improve user satisfaction.

Questions remain whether or not adolescents using DMPA or Depo-subQ will achieve normal peak levels of bone density or whether long-term use will result in significant bone loss. A black-box warning in the package insert warns that the use of DMPA or Depo-subQ should be limited to 2 years of use or less, unless other methods are inadequate. Although adolescents are counseled about this warning, especially with long-term use, it is important to keep this risk balanced with the social, psychological, and medical risks of unintended pregnancy.

WHO guidelines suggest that the benefits of use of DMPA in adolescents under 18 outweigh the risks.

Some very reassuring papers concerning the long-term safety of DMPA have been published. The use of DMPA does not appear to increase the risk of osteoporosis later in life. In a cohort study of 170 adolescents, bone mineral density (BMD) was completely recovered 12 months post-DMPA discontinuation [50]. In fact, the adjusted mean BMD values at all anatomic sites at 12 months after discontinuation of DMPA were as high as or higher than those of nonusers. In a randomized, double-blind controlled trial of 123 adolescents, low-dose estradiol supplementation to DMPA use resulted in no decline in BMD [51].

These findings are similar to the findings associated with lactation showing that bone losses associated with lactation are reversible and do not lead to long-term skeletal changes [52]. The bone loss occurring in both teenage and adult DMPA users is probably the result of the contraceptive-induced reduction in ovarian estradiol production [53]. For healthcare providers, this is reassuring information. Although it is rarely necessary to monitor bone loss with bone imaging studies, calcium supplementation is recommended for most teenagers, regardless of contraceptive choice. Calcium supplementation plus adequate exercise may substantially reduce the risk of bone loss when on DMPA therapy. Estrogen supplementation is generally unnecessary because full recovery of bone density is expected after discontinuation.

The new POP containing 4-mg drospirenone is now marketed. The 24-4 regimen and higher progestin dose is designed to better control bleeding (compared to the daily norethindrone POP). It also can be taken at any time during the day.

Emergency Contraception

Appropriate counseling for sexually active adolescents includes information regarding the availability of emergency contraception and how to get it. Plan B is a levonorgestrel pill, available over the counter, that should be taken within 3 days of

unprotected intercourse (less effectiveness if taken days 3 through 5). Plan B may alter the next menstrual period as it may be earlier, later, lighter, or heavier. If emesis occurs within 2 hours of taking the pill, another pill should be taken. The pill may cause upset stomach, lightheadedness, or tender breasts for a short period of time. Ella is a prescription medication that is obtained with a prescription and is effective up to 5 days after unprotected intercourse.

Perimenopausal Women

Recommended: Hormonal LARCs, POPs (including the new drospirenone POP), and DMPA, and in selected patients low-dose or very-low-dose [10 μg] COCPs, copper-IUD, or barriers

Women in perimenopause are entering a final phase of reproductive life that is associated with lowered risk of pregnancy, changes in menstrual bleeding patterns, and "roller-coaster" changes in ovarian hormone production. In many patients, long-standing health issues may be associated with early physical changes that may eventually lead to serious health problems, including osteoporosis, cardiovascular disease (CVD), or cancer. Consideration of these risk factors may be important when selecting a contraceptive method, as well as intervention strategies, for these women.

Many women in perimenopause, especially those with irregular menses, believe they are no longer fertile and therefore tend not to use contraceptive protection [54]. Although fertility is decreased and pregnancy rates are low in this age group, sexually active perimenopausal women may still be at risk. Even with menstrual irregularities, some women may have sporadic ovulation [55] and thus some risk of pregnancy. If pregnancy occurs in this age group, it is often unintended and unwanted. Pregnant women over age 40 have one of the highest induced abortion rates, surpassed only by pregnant teenagers [56].

Women of ages 35–44 now constitute the largest single group of reproductive-aged women in the United States. As these older women seek contraceptive counseling, many noncontraceptive benefits of hormonal contraceptives become increasingly more relevant.

Concerns: Breast or Other Cancer Risks

The risk of breast cancer is addressed above ("Counseling General Reproductive-Aged User: Concerns – Cancer Risk"). Overall, multiple studies report either undetectable or very low increase in risk that is further decreased over time after discontinuation combination of oral contraceptives. This risk should be discussed with the evidence that various contraceptive methods reduce the risk of endometrial, ovarian, and colorectal cancer (Table 14.1).

Concerns: Perimenopausal Bleeding Problems

Perimenopausal women often have changes in their bleeding patterns as they enter the perimenopause and progress toward menopause. They may experience shorter or longer cycles, heavier or lighter periods, and eventually irregular or skipped periods. Sexually active transitional women with irregular cycles or heavy periods are particularly good candidates for progestin-containing hormonal contraceptive methods including LNG-20 IUD, implant, Depo-Provera, and progestin-only pills (particularly the new drosperinone-only option. While combination low-dose OCs are highly effective and generally safe, care must be taken that potential users do not have any of the red flag warnings for women over age 35 (hypertension, smoking, migraine headaches, long-standing diabetes, or other significant CVD risk factors).

Concerns: Perimenopausal Symptoms

Many women during the transition to menopause experience at least one of the common perimenopausal symptoms. These symptoms include sleep disturbances, hot flashes, mood changes, vaginal dryness, headaches, "the fog," and dyspareunia [57]. In a population-based prospective cohort study, 31% of African American and Caucasian women 35–47 years of age at entry reported having hot flashes [58]. Healthy, sexually active, symptomatic transitional women without red flag warning are candidates for low-dose COCs or rings. COCs are the best studied of the CHCMs. Numerous trials report that COCs reduce hot flashes, improve vaginal dryness, and decrease sleep disturbances in symptomatic transitional women [59]. The use of the COCs with reduced pill-free days [24-4] or adding a low-dose estradiol pill or patch during the pill-free days avoids the return of symptoms during these days. However, careful review of red flag risk factors must be done prior to use. The use of LARC methods or progestin only pills [including the drosperinone containg POP] plus addition of low-dose hormone replacement is often a safe option.

Concerns: Decline of BMD

From age 30, there is a slow but often steady decline in BMD in women that generally accelerates during the final years of the transition and early menopause. The use of combination hormonal contraceptives may prevent or lessen this loss.

In an analysis of 13 studies reporting on BMD and low-dose OCs, nine showed a positive effect and four showed a neutral effect [60]. In a 2-year randomized study of women aged 40–48, calcium-only was associated with a 3.4% decrease in BMD, whereas low-dose OCs had a 1.71% significant increase [61]. 58 In a case–control study, postmenopausal women who used OCs at age 40 or older had a significantly decreased risk of postmenopausal hip fracture (odds ratio 0.69, confidence interval 0.51, 0.94) compared with nonusers [62]. But

again, in women over 35, special care must be done to ensure there are no red flag contraindications to COCPs (as discussed above and in Chap. 2) as there are significant risks, particularly in selected users, as discussed below.

Ensuring adequate calcium and vitamin D intake, encouraging weight-bearing activities (like walking down steps), and discussing risks and benefits of HRT in the perimenopause and menopause are recommended.

Concerns: Cardiovascular Risks

The major two concerns, especially of older reproductive-aged women, are risk of myocardial infarction and risk of breast cancer. There is a substantial body of evidence that although current use of low-dose OCs increases the risk of venous thromboembolism, the risk of myocardial infarction and stroke is not increased in nonsmoking, nonhypertensive current or past users [63–65]. This data is reassuring that with careful selection of healthy, nonsmoking, normotensive perimenopausal women without migraine headaches, low-dose OCs can be used for contraceptive protection [66, 67].

In 2011, the FDA released a drug safety report of the results of a study of more than 800,000 users of the contraceptive vaginal ring. This report found that ring users had an increased risk of venous thromboembolism compared with users of low-dose oral contraceptives [68]. However, a prospective, controlled, non-interventional cohort study performed in the United States and five European countries compared the vaginal ring to combined OCP users. Study participants were followed for over 66,000 woman-years. The authors concluded that vaginal ring use and combined OCP use were associated with a similar venous and arterial thromboembolic risk during routine clinical use [69].

Whether or not some of the progestin-only contraceptives increase the risk of VTE is unclear [70–72]. The levonorgestrel-releasing IUD does not increase the risk of VTE.

Contraceptive Options

1. IUDs are good contraceptive choices for perimenopausal women with a normal endometrial cavity. IUDs are a particularly good option for older smoking women and those with cardiovascular risk factors, known CV disease, or migraine headache (since COCs are generally not an option when these factors are present).
   (a) There are five currently available IUDs in the United States: the copper T 380A (ParaGard®) provides 10 years of contraceptive protection, the LNG-20 (Mirena® and Liletta) provides 5 years of protection, the LNG-17.5 IUD (Kyleena) provides 5 years of protection, and the LNG-14 (Skyla) provides 3 years of protection.

The LNG-20 (and to a slightly lesser degree the other LNG-releasing IUDs) adds an important noncontraceptive advantage for this age group: it decreases menstrual blood loss and dysmenorrhea and may avoid the need for hysterectomy or endometrial ablation (*see bleeding concerns above*). The use of the LNG-20 IUD is reported to reduce the risk of endometrial cancer by 40–60% (Table 14.1).

The copper IUD is generally associated with heavier menses but is highly effective, has few contraindications for use (okay after breast cancer), and lasts for at least 10 years.

2. Combination OCs may reduce perimenopausal symptoms, such as hot flashes, sleep disturbances, bone loss, and vaginal dryness [73]. The prescribing choice should be formulations containing the lowest amount of estrogen and progestin (preferably ≤20-μg estrogen OCs), particularly those that have a shortened pill-free intervals. Some perimenopausal women may develop hot flashes or other perimenopausal symptoms during the pill-free interval, and switching to an OC with a shortened pill-free interval may alleviate these problems.

   (a) If they are not sexually active, there is no need to add a contraceptive option. Continuous low-dose estrogen-only therapy (hormonal replacement pills or patches which are approved to reduce hot flashes in menopausal women) may be used in symptomatic perimenopausal women complaining of hot flashes, sleeping problems, or mood changes. If sexually active, the prescribing choice should be formulations containing the lowest amount of estrogen and progestin (preferably ≤20-μg estrogen OCs or rings), particularly those that have a shortened pill-free intervals.

   Because of a lowered fecundity and better adherence [74], older women using OCs tend to have very low rates of unintended pregnancies [75].

   The use of OCs also regulates bleeding patterns, an important benefit for many women in transition in which dysfunctional uterine bleeding is common [76]. Combination OCs may reduce the amount of blood loss by 44% [77] and protect from the development of endometrial cancer (Table 14.1).

3. Progestin-Only Methods: Depo-Provera (DMPA and Depo-subQ) and POP (particularly the new drospirenone POP). The progestin-only methods Depo-Provera, Depo-subQ, mini-pills, and implants are generally safe in women of any age, regardless of whether or not the patient smokes or has CVD (with the exception of Depo-Provera which is category 3 for known CVD). Although these progestin-only methods tend to decrease menstrual blood loss, they can be associated with unpredictable bleeding patterns. (Note new drosperinone only pill is associated with good bleeding control). Transitional women with heavy blood loss may welcome the reduction in overall blood or possibility that they may have amenorrhea, a finding in 55% of DMPA users after 1 year of use [78–80]:

(a) The use of a progestin contraceptive in perimenopausal women with irregular cycles often adds needed protection from unopposed estrogen and its associated increased risk of endometrial hyperplasia. Ever use of DMPA is associated with a 79% reduction in the risk of endometrial cancer (Table 14.1).
(b) Symptomatic women with hot flashes may consider DMPA as it is associated with a reduction in hot flashes [81]. There is always a concern about bone density after long-term use of DMPA, and the black-box warning suggests a limit of 2 years. In some patients, however, the overall risk–benefit profile may favor continued use. Of positive note is one study reporting that the use of DMPA from age 25 to menopause reduced early menopausal bone loss in the spine and hip compared with controls [82]. On the negative side, the use of DMPA may be associated with a tendency for weight gain in some users.
(c) The newly released drospirenone POP contains a large dose of drospirenone (4 mg) and is designed in a 24-4 protocol to reduce and control bleeding patterns. A potential reduction in hirsutism or acne may be an advantage of this method.

4. CVRs are an option for healthy, sexually active perimenopausal women who are nonsmokers and normotensive and have no significant risk factors for CVD or migraine headaches. The CVR often improves bleeding control and may lessen perimenopausal symptoms. Some perimenopausal women may develop hot flashes or other perimenopausal symptoms during the ring-free interval, and using the CVR continuously is an option.
5. Sterilization: For perimenopausal women who have finished their childbearing and choose not to use LARC methods, a tubal ligation is an option. The newer forms of tubal sterilization (Essure® and Adiana Systems) have largely been discontinued. For women with a stable relationship, male vasectomy is also an option.
6. Barrier Methods: Perimenopausal women seeking contraceptive protection who have recently undergone lifestyle changes, such as widowhood or divorce, may be at risk of having multiple sexual partners and may want to consider male or female condom use. For a transitional-aged woman who is in a stable relationship and does not have significant uterine or vaginal prolapse owing to multiple childbirths, the diaphragm and cervical cap are options. As in any age group, selecting the method the patient is most likely to use correctly and consistently is the goal.
7. Emergency Contraception: Regardless of the method chosen, it is important to offer counseling regarding availability and how to access emergency contraception (see above).
8. Natural Family Planning: Irregular menstrual cycles may make this method more difficult for the perimenopausal patient.

Patient Screening and Choosing a Combination Hormonal Method for Perimenopausal Women

For women of all ages, the LARC methods are first-line options. In normotensive, nonsmoking, healthy perimenopausal women without significant risk factors for CVD

or thrombosis, the lowest dose OCs and rings can be used until fertility is no longer an issue. Measurement of an FSH >20 mIU/ml indicates late perimenopausal status and a very low to no risk of pregnancy (see below). Evaluating a perimenopausal woman for a safe, appropriate contraceptive method includes investigating the following:

- Health conditions, especially known CVD, significant risk factors for CVD including duration and severity, clotting problems, previous thromboembolic events (see below)
- Gynecological issues
  - Sexual activity: need for contraception
  - Bleeding problems and need for bleeding control
  - Degree of perimenopausal symptoms
  - Other gynecological problems, such as fibroids and endometriosis

Contraindications for use in this older population (>35 years of age) include the following:

- Known CVD or significant risk factors for vascular disease.
- Hypertension (controlled or not), cigarette smoking, diabetes, long-standing insulin resistance, long-standing lipid abnormalities, statin therapy, long-standing obesity, and systemic disease that affects the vascular system (such as lupus erythematosus)
- History of significant clotting problems: thromboembolism, thrombophlebitis, deep vein thrombosis, pulmonary embolism, or known thrombogenic mutation
- Current or history of cancer of the breast
- Migraine headaches (with or without aura or localizing signs)
- Current gallbladder disease
- Active moderate or severe liver disease
- Prolonged immobilization, impending major surgery
- Current pregnancy

Noncontraceptive Benefits of Low-Dose OCs in Perimenopausal Women

OCs and presumably other combination products offer a number of important noncontraceptive benefits. As discussed previously, these benefits may include the following:

- Controlled bleeding
- Lowered risk for anemia
- Lowering the risk of ovarian cancer, endometrial cancer, and possibly colorectal cancer (Table 14.1)
- Decreasing the loss of bone density
- Decreasing symptoms of perimenopause: less hot flashes, vaginal dryness, and atrophy
- Lowered risk for ectopic pregnancy

When It Is Safe to Discontinuing OCs or Switch to Hormone Therapy

Women now continue OCs into their 40s, and unfortunately there is no "fail-safe" method in determining when it is safe to discontinue OCs or switch to hormone therapy. However, the following protocols are suggested:

- Begin checking follicle-stimulating hormone (FSH) annually after age 45 on day 6 of placebo pills; discontinue OCs when FSH is 20 mIU/ml or higher.
- For women with a dramatic drop in bleeding and/or development of hot flushes during the pill-free intervals, check FSH on day 6 or after 2 weeks off OCs; an increased FSH 20 mIU/ml or higher indicates it is safe to discontinue [83].

Postpartum and During Lactation

Recommended: LARC methods and progestin-only methods are first-line options – other first-line options depend on health issues and breastfeeding plans.

Choosing the right contraceptive method following pregnancy has a lot to do with whether a full-term pregnancy has occurred and whether or not a potential user plans to breastfeed. A major issue regarding contraception use following pregnancy is when to begin.

Timing of Initiation

The return of ovulation is different in women following a full-term pregnancy compared with a first-trimester pregnancy loss, and the recommendations are different (Table 14.5). Following a term delivery, the suppression of ovulation is prolonged and the first bleeding episode is usually, but not always, anovulatory.

In a non-breastfeeding woman, ovulation is usually delayed until 6 weeks postpartum, but it can occur as early as 4 weeks. The use of CHCM (products containing estrogen) should be delayed to 4 weeks postpartum due to increased VTE risk during the immediate postpartum period. Women who are breastfeeding exclusively every 4 hours, including during the night, will not ovulate until at least 10 weeks postpartum and often as long as 6 months postpartum.

Following a spontaneous or induced first-trimester abortion, ovulation usually occurs within 2–4 weeks. The first month following a first-trimester pregnancy loss is usually an ovulatory cycle and pregnancy can occur.

Table 14.5 Updated CDC's US medical eligibility criteria for contraceptive use in postpartum patients and history of past ectopic [84]

		CHCM	POP	DMPA	ETO-implant	LNG-IUD	Cu IUD
Postabortion	1st trimester	1	1	1	1	1	1
	2nd trimester	1	1	1	1	2	2
	Immediate post-septic	1	1	1	1	4	4
Postpartum after delivery of placenta breastfeeding or not including C-section	<10 minutes					2	1
	10 min to <4 weeks					2	2
	≥4 weeks					1	1
	Puerperal sepsis					4	4
	<21 days	4	1	1	1		
	21–42 days with other risk factors VTE	3	1	1	1		
	21–42 days no other risk factors VTE	2	1	1	1		
	>42 days	1	1	1	1		
Postpartum breastfeeding	<1 month postpartum	3	2	2	2		
	>1 month postpartum	2	1	1	1		
Past ectopic pregnancy		1	2	1	1	1	1

Beginning a contraceptive immediately is recommended following a first- or second-trimester pregnancy loss.

- Delaying the start of a combination hormonal contraceptive avoids further enhancement of thrombophilic risk during the postpartum period in which the risk is already increased.
  - Waiting 4–6 weeks after delivery has been shown to be safe and will not adversely affect infant health and growth when used in breastfeeding users.
- Immediate postplacental placement of an IUD or insertion of subdermal implant is now an option. The other option is to wait 4–6 weeks into the postpartum period for IUD insertion, thus allowing the uterus to return to normal size and reducing the risk of spontaneous IUD expulsion.
- Delaying use of a diaphragm or cervical cap until after bleeding and lochia abates is recommended.

Contraceptive Options

1. *ETO-implant* Nexplanon® contraceptive implants contain the progestin etonogestrel. Unlike the previously marketed Norplant®, these implants contain a single rod and are supplied in an insertor. Insertion and removal are in-office minor procedures. These implants offer high efficacy protection for up to 3 years. The contraceptive implant is one of the preferred LARC methods that are first-line options.
2. *IUD*: The other LARC preferred option is the IUDs. The copper-containing or LNG-releasing IUDs are excellent options for postpartum women that would like to space their pregnancies. Heavier periods following insertion of the copper-containing device and lighter periods following insertion of the LNG-releasing IUD can be expected.
3. *Progestin-only methods* including the new drospirenone POP are generally safe, decrease bleeding, and offer good contraceptive protection.
4. *Barriers*: In the postpartum period, sexual activity may be less frequent, and the on-hand protection provided by barriers may be sufficient. Some women particularly like the idea of a noninvasive, nonhormonal method during this period. The female and male condoms offer protection from STDs and are recommended in women who are at risk. Women in the immediate postpartum period or those who are breastfeeding may have vaginal dryness and appreciate the lubrication of vaginal spermicides. The use of a diaphragm or cap is recommended after bleeding and lochia has abated.
5. *Tubal Ligation or Salpingectomy*: The traditional tubal ligation or bilateral salpingectomy is done at the time of cesarian section, in the immediate postpartum period, or as an interim procedure. Success rate is high. The use of micro-implants into the fallopian tubes is now not done due to high side effect profile and failure rates.

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Chapter 15
Contraception for Women with Medical Conditions

Anita L. Nelson

Introduction

Providing contraception to women with medical problems is more challenging than providing such care to healthy women, because the health risks of contraceptive use are often greater for women with medical problems. *However, these contraceptive risks are clearly overshadowed by the health risks the women would face with pregnancy.*

Each year, over 700 US women die from pregnancy and pregnancy-related causes [1] and another 50,000 US women suffer "near misses" or "severe morbidity" [2]. Health problems are greatly magnified by socioeconomic factors; minority women are disproportionately at risk for death during pregnancy [3]. Tragically, at least 45% of the women who suffer such outcomes did not want to become pregnant at the time they conceived; unintended pregnancy rates are higher among adult women with medical conditions compared to healthy women [4, 5]. Recent fiscal and legislative changes reducing women's access to family planning and reproductive health services have contributed to increased maternal mortality ratios observed in the United States, while those ratios have declined in most other developed and developing countries [6].

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Patient Counseling

The gold standard for contraceptive counseling is the patient-centered, shared decision-making model, which is founded on the patient's personal preferences and values and is designed to preserve her autonomy [7].

The approach relies on the fact that the patient knows about all her options and that she has (access to) adequate information to make an informed choice. It is particularly important that women with medical conditions understand the health risks that pregnancy presents to them and the impacts their conditions might have on the wellbeing of their fetus. Models for this counseling have been well described and field tested [8].

In this chapter, the word "woman" is used as shorthand to represent a person who is at risk for pregnancy, regardless of that person's gender identity. It is hoped that readers will understand that distinction and recognize that, in practice, people with a wide range of different gender identities will present with health problems and need pregnancy protection.

Chronic medical problems are quite common among reproductive age women in the United States. A recent survey of over 700,000 16–49-year-old US women in the intermountain region revealed that 32% had one chronic health condition and 7.3% had at least two. *Highly effective contraceptive methods were used by 5.8% of women with chronic conditions* [9].

Similar national surveys of privately insured women confirm that contraceptive use is not optimal among women with medical conditions [10]. Many primary care providers significantly underestimate the rates of unintended pregnancy and the risk of pregnancy [11]. Women with medical conditions may also underestimate their own needs for contraception; they may misunderstand their provider's counseling and believe they are completely infertile and do not require contraception. Institutional and religious barriers may also influence reproductive care counseling and availability [12, 13].

Role of Contraception

Contraception provides all women with the ability to reduce their risk for unwanted pregnancies, and it provides women time to prepare for wanted pregnancies to insure the healthiest possible maternal and fetal outcomes. Specialized preconception care is frequently needed to optimize the woman's health, to minimize teratogenic exposures, and to prepare her for the challenges pregnancy will present. In

addition, contraceptive methods can offer women non-contraceptive health benefits to minimize some of the health impacts of their medical conditions and their side effects of the treatments for those conditions. On the other side of the ledger, the impacts that the method or its potential side effects may have on the medical condition or treatments must also be assessed.

Historical Barriers

Information about the appropriateness of use of different methods of contraception by woman with medical problems has accumulated slowly over time for several reasons. *Answers are not available from the pivotal clinical trials because only healthy women are enrolled into those studies*.

Family planning experts often have only limited experience providing contraception to women with specific medical conditions. Experts in treating specific medical conditions do not usually address contraceptive needs [14]. As a result, the lack of sufficient experience has historically led to relatively restrictive practice recommendations and to extensive lists of contraindications to methods based primarily on theoretical health or liability-based concerns. For example, when the copper IUD was reintroduced in 1988, immunocompromising conditions, such as diabetes, steroid use, and chemotherapy, were listed as contraindications to its use. Similarly, in the past, women with risk factors for venous thromboembolism were advised to avoid all "hormonal methods" including progestin-only methods. And for many years, all women over 35 (even healthy non-smokers) were not allowed to use estrogen-containing methods. So much has changed since then.

Resources

Fortunately, today we have evidence-based guidelines developed by teams of contraceptive experts assembled by the CDC, who periodically review the literature and customize the World Health Organization's Medical Eligibility Criteria and Selected Practice Recommendations to serve American couples and to address the medical problems more commonly seen in the United States. The resulting documents, the US Medical Eligibility Criteria for Contraceptive Use, 2016 (US MEC), and Selective Practice Recommendation for Contraceptive Use, 2016 (SPR) are readily available online at https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm.

The summary table of the US MEC, which is included as Fig. 15.1, answers the question of "who" can use each prescription method. For each medical condition, a woman's eligibility for each of those methods is rated on a scale from 1 (no restrictions) to 4 (unacceptable health risks). In between are the two other possibilities:

Category 2 (advantages generally outweigh theoretical or proven risks) and Category 3 (theoretical or proven risks usually outweigh the advantages). Category 3 does not prohibit method use, especially when all the alternatives may pose even greater health risks. The US Selected Practice Recommendations for Contraceptive Use, 2016 provides the "how" to use the different methods (after a complete history has revealed no contraindications) by answering the following questions: What physical

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Age		Menarche to <20 yrs: **2**		Menarche to <20 yrs: **2**		Menarche to <18 yrs: **1**		Menarche to <18 yrs: **2**		Menarche to <18 yrs: **1**		Menarche to <40 yrs: **1**	
		≥20 yrs: **1**		≥20 yrs: **1**		18-45 yrs: **1**		18-45 yrs: **1**		18-45 yrs: **1**		≥40 yrs: **2**	
						>45 yrs: **1**		>45 yrs: **2**		>45 yrs: **1**			
Anatomical abnormalities	a) Distorted uterine cavity	**4**		**4**									
	b) Other abnormalities	**2**		**2**									
Anemias	a) Thalassemia	**2**		**1**		**1**		**1**		**1**		**1**	
	b) Sickle cell disease‡	**2**		**1**		**1**		**1**		**1**		**2**	
	c) Iron-deficiency anemia	**2**		**1**		**1**		**1**		**1**		**1**	
Benign ovarian tumors	(*including cysts*)	**1**		**1**		**1**		**1**		**1**		**1**	
Breast disease	a) Undiagnosed mass	**1**		**2**		**2***		**2***		**2***		**2***	
	b) Benign breast disease	**1**		**1**		**1**		**1**		**1**		**1**	
	c) Family history of cancer	**1**		**1**		**1**		**1**		**1**		**1**	
	d) Breast cancer‡												
	i) Current	**1**		**4**		**4**		**4**		**4**		**4**	
	ii) Past and no evidence of current disease for 5 years	**1**		**3**		**3**		**3**		**3**		**3**	
Breastfeeding	a) <21 days postpartum					**2***		**2***		**2***		**4***	
	b) 21 to <30 days postpartum												
	i) With other risk factors for VTE					**2***		**2***		**2***		**3***	
	ii) Without other risk factors for VTE					**2***		**2***		**2***		**3***	
	c) 30-42 days postpartum												
	i) With other risk factors for VTE					**1***		**1***		**1***		**3***	
	ii) Without other risk factors for VTE					**1***		**1***		**1***		**2***	
	d) >42 days postpartum					**1***		**1***		**1***		**2***	
Cervical cancer	Awaiting treatment	**4**	**2**	**4**	**2**	**2**		**2**		**1**		**2**	
Cervical ectropion		**1**		**1**		**1**		**1**		**1**		**1**	
Cervical intraepithelial neoplasia		**1**		**2**		**2**		**2**		**1**		**2**	
Cirrhosis	a) Mild (*compensated*)	**1**		**1**		**1**		**1**		**1**		**1**	
	b) Severe‡ (*decompensated*)	**1**		**3**		**3**		**3**		**3**		**4**	
Cystic fibrosis‡		**1***		**1***		**1***		**2***		**1***		**1***	
Deep venous thrombosis (DVT)/Pulmonary embolism (PE)	a) History of DVT/PE, not receiving anticoagulant therapy												
	i) Higher risk for recurrent DVT/PE	**1**		**2**		**2**		**2**		**2**		**4**	
	ii) Lower risk for recurrent DVT/PE	**1**		**2**		**2**		**2**		**2**		**3**	
	b) Acute DVT/PE	**2**		**2**		**2**		**2**		**2**		**4**	
	c) DVT/PE and established anticoagulant therapy for at least 3 months												
	i) Higher risk for recurrent DVT/PE	**2**		**2**		**2**		**2**		**2**		**4***	
	ii) Lower risk for recurrent DVT/PE	**2**		**2**		**2**		**2**		**2**		**3***	
	d) Family history (*first-degree relatives*)	**1**		**1**		**1**		**1**		**1**		**2**	
	e) Major surgery												
	i) With prolonged immobilization	**1**		**2**		**2**		**2**		**2**		**4**	
	ii) Without prolonged immobilization	**1**		**1**		**1**		**1**		**1**		**2**	
	f) Minor surgery without immobilization	**1**		**1**		**1**		**1**		**1**		**1**	
Depressive disorders		**1***		**1***		**1***		**1***		**1***		**1***	

Key:	
1 No restriction (method can be used)	**3** Theoretical or proven risks usually outweigh the advantages
2 Advantages generally outweigh theoretical or proven risks	**4** Unacceptable health risk (method not to be used)

Fig. 15.1 US MEC Summary Table

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Diabetes	a) History of gestational disease	1		1		1		1		1		1	
	b) Nonvascular disease												
	i) Non-insulin dependent	1		2		2		2		2		2	
	ii) Insulin dependent	1		2		2		2		2		2	
	c) Nephropathy/retinopathy/neuropathy‡	1		2		2		3		2		3/4*	
	d) Other vascular disease or diabetes of >20 years' duration‡	1		2		2		3		2		3/4*	
Dysmenorrhea	Severe	2		1		1		1		1		1	
Endometrial cancer‡		4	2	4	2	1		1		1		1	
Endometrial hyperplasia		1		1		1		1		1		1	
Endometriosis		2		1		1		1		1		1	
Epilepsy‡	(*see also Drug Interactions*)	1		1		1*		1*		1*		1*	
Gallbladder disease	a) Symptomatic												
	i) Treated by cholecystectomy	1		2		2		2		2		2	
	ii) Medically treated	1		2		2		2		2		3	
	iii) Current	1		2		2		2		2		3	
	b) Asymptomatic	1		2		2		2		2		2	
Gestational trophoblastic disease‡	a) Suspected GTD (immediate postevacuation)												
	i) Uterine size first trimester	1*		1*		1*		1*		1*		1*	
	ii) Uterine size second trimester	2*		2*		1*		1*		1*		1*	
	b) Confirmed GTD												
	i) Undetectable/non-pregnant ß-hCG levels	1*	1*	1*	1*	1*		1*		1*		1*	
	ii) Decreasing ß-hCG levels	2*	1*	2*	1*	1*		1*		1*		1*	
	iii) Persistently elevated ß-hCG levels or malignant disease, with no evidence or suspicion of intrauterine disease	2*	1*	2*	1*	1*		1*		1*		1*	
	iv) Persistently elevated ß-hCG levels or malignant disease, with evidence or suspicion of intrauterine disease	4*	2*	4*	2*	1*		1*		1*		1*	
Headaches	a) Nonmigraine (mild or severe)	1		1		1		1		1		1*	
	b) Migraine												
	i) Without aura (includes menstrual migraine)	1		1		1		1		1		2*	
	ii) With aura	1		1		1		1		1		4*	
History of bariatric surgery‡	a) Restrictive procedures	1		1		1		1		1		1	
	b) Malabsorptive procedures	1		1		1		1		3		COCs: 3 P/R: 1	
History of cholestasis	a) Pregnancy related	1		1		1		1		1		2	
	b) Past COC related	1		2		2		2		2		3	
History of high blood pressure during pregnancy		1		1		1		1		1		2	
History of Pelvic surgery		1		1		1		1		1		1	
HIV	a) High risk for HIV	1*	1*	1*	1*	1		1		1		1	
	b) HIV infection					1*		1*		1*		1*	
	i) Clinically well receiving ARV therapy	1	1	1	1	If on treatment, see Drug Interactions							
	ii) Not clinically well or not receiving ARV therapy‡	2	1	2	1	If on treatment, see Drug Interactions							

Abbreviations: ARV = antiretroviral; C=continuation of contraceptive method; CHC=combined hormonal contraception (pill, patch, and, ring); COC=combined oral contraceptive; Cu-IUD=copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; I=initiation of contraceptive method; LNG-IUD=levonorgestrel-releasing intrauterine device; NA=not applicable; POP=progestin-only pill; P/R=patch/ring; SSRI=selective serotonin reuptake inhibitor; ‡ Condition that exposes a woman to increased risk as a result of pregnancy. *Please see the complete guidance for a clarification to this classification: https://www.cdc.gov/reproductivehealth/contraception/contraception_guidance.htm.

Fig. 15.1 (continued)

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Hypertension	a) Adequately controlled hypertension	1*		1*		1*		2*		1*		3*	
	b) Elevated blood pressure levels (*properly taken measurements*)												
	i) Systolic 140-159 or diastolic 90-99	1*		1*		1*		2*		1*		3*	
	ii) Systolic ≥160 or diastolic ≥100‡	1*		2*		2*		3*		2*		4*	
	c) Vascular disease	1*		2*		2*		3*		2*		4*	
Inflammatory bowel disease	(*Ulcerative colitis, Crohn's disease*)	1		1		1		2		2		2/3*	
Ischemic heart disease‡	Current and history of	1		2	3	2	3	3		2	3	4	
Known thrombogenic mutations‡		1*		2*		2*		2*		2*		4*	
Liver tumors	a) Benign												
	i) Focal nodular hyperplasia	1		2		2		2		2		2	
	ii) Hepatocellular adenoma‡	1		3		3		3		3		4	
	b) Malignant‡ (hepatoma)	1		3		3		3		3		4	
Malaria		1		1		1		1		1		1	
Multiple risk factors for atherosclerotic cardiovascular disease	(e.g., older age, smoking, diabetes, hypertension, low HDL, high LDL, or high triglyceride levels)	1		2		2*		3*		2*		3/4*	
Multiple sclerosis	a) With prolonged immobility	1		1		1		2		1		3	
	b) Without prolonged immobility	1		1		1		2		1		1	
Obesity	a) Body mass index (BMI) ≥30 kg/m²	1		1		1		1		1		2	
	b) Menarche to <18 years and BMI ≥ 30 kg/m²	1		1		1		2		1		2	
Ovarian cancer‡		1		1		1		1		1		1	
Parity	a) Nulliparous	2		2		1		1		1		1	
	b) Parous	1		1		1		1		1		1	
Past ectopic pregnancy		1		1		1		1		2		1	
Pelvic inflammatory disease	a) Past												
	i) With subsequent pregnancy	1	1	1	1	1		1		1		1	
	ii) Without subsequent pregnancy	2	2	2	2	1		1		1		1	
	b) Current	4	2*	4	2*	1		1		1		1	
Peripartum cardiomyopathy‡	a) Normal or mildly impaired cardiac function												
	i) <6 months	2		2		1		1		1		4	
	ii) ≥6 months	2		2		1		1		1		3	
	b) Moderately or severely impaired cardiac function	2		2		2		2		2		4	
Postabortion	a) First trimester	1*		1*		1*		1*		1*		1*	
	b) Second trimester	2*		2*		1*		1*		1*		1*	
	c) Immediate postseptic abortion	4		4		1*		1*		1*		1*	
Postpartum (*nonbreastfeeding women*)	a) <21 days					1		1		1		4	
	b) 21 days to 42 days												
	i) With other risk factors for VTE					1		1		1		3*	
	ii) Without other risk factors for VTE					1		1		1		2	
	c) >42 days					1		1		1		1	
Postpartum (*in breastfeeding or nonbreastfeeding women, including cesarean delivery*)	a) <10 minutes after delivery of the placenta												
	i) Breastfeeding	1*		2*									
	ii) Nonbreastfeeding	1*		1*									
	b) 10 minutes after delivery of the placenta to <4 weeks	2*		2*									
	c) ≥4 weeks	1*		1*									
	d) Postpartum sepsis	4		4									

Fig. 15.1 (continued)

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant	DMPA	POP	CHC
		I	C	I	C	I C	I C	I C	I C
Pregnancy		4*		4*		NA*	NA*	NA*	NA*
Rheumatoid arthritis	a) On immunosuppressive therapy	2	1	2	1	1	2/3*	1	2
	b) Not on immunosuppressive therapy	1		1		1	2	1	2
Schistosomiasis	a) Uncomplicated	1		1		1	1	1	1
	b) Fibrosis of the liver‡	1		1		1	1	1	1
Sexually transmitted diseases (STDs)	a) Current purulent cervicitis or chlamydial infection or gonococcal infection	4	2*	4	2*	1	1	1	1
	b) Vaginitis (*including trichomonas vaginalis and bacterial vaginosis*)	2	2	2	2	1	1	1	1
	c) Other factors relating to STDs	2*	2	2*	2	1	1	1	1
Smoking	a) Age <35	1		1		1	1	1	2
	b) Age ≥35, <15 cigarettes/day	1		1		1	1	1	3
	c) Age ≥35, ≥15 cigarettes/day	1		1		1	1	1	4
Solid organ transplantation‡	a) Complicated	3	2	3	2	2	2	2	4
	b) Uncomplicated	2		2		2	2	2	2*
Stroke‡	History of cerebrovascular accident	1		2		2 3	3	2 3	4
Superficial venous disorders	a) Varicose veins	1		1		1	1	1	1
	b) Superficial venous thrombosis (acute or history)	1		1		1	1	1	3*
Systemic lupus erythematosus‡	a) Positive (or unknown) antiphospholipid antibodies	1*	1*	3*		3*	3* 3*	3*	4*
	b) Severe thrombocytopenia	3*	2*	2*		2*	3* 2*	2*	2*
	c) Immunosuppressive therapy	2*	1*	2*		2*	2* 2*	2*	2*
	d) None of the above	1*	1*	2*		2*	2* 2*	2*	2*
Thyroid disorders	Simple goiter/ hyperthyroid/hypothyroid	1		1		1	1	1	1
Tuberculosis‡ *(see also Drug Interactions)*	a) Nonpelvic	1	1	1	1	1*	1*	1*	1*
	b) Pelvic	4	3	4	3	1*	1*	1*	1*
Unexplained vaginal bleeding	(suspicious for serious condition) before evaluation	4*	2*	4*	2*	3*	3*	2*	2*
Uterine fibroids		2		2		1	1	1	1
Valvular heart disease	a) Uncomplicated	1		1		1	1	1	2
	b) Complicated‡	1		1		1	1	1	4
Vaginal bleeding patterns	a) Irregular pattern without heavy bleeding	1		1	1	2	2	2	1
	b) Heavy or prolonged bleeding	2*		1*	2*	2*	2*	2*	1*
Viral hepatitis	a) Acute or flare	1		1		1	1	1	3/4* 2
	b) Carrier/Chronic	1		1		1	1	1	1 1
Drug Interactions									
Antiretrovirals used for prevention (PrEP) or treatment of HIV	Fosamprenavir (FPV) All other ARVs are 1 or 2 for all methods.	1/2*	1*	1/2*	1*	2*	2*	2*	3*
Anticonvulsant therapy	a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	1		1		2*	1*	3*	3*
	b) Lamotrigine	1		1		1	1	1	3*
Antimicrobial therapy	a) Broad spectrum antibiotics	1		1		1	1	1	1
	b) Antifungals	1		1		1	1	1	1
	c) Antiparasitics	1		1		1	1	1	1
	d) Rifampin or rifabutin therapy	1		1		2*	1*	3*	3*
SSRIs		1		1		1	1	1	1
St. John's wort		1		1		2	1	2	2

Updated in 2020. This summary sheet only contains a subset of the recommendations from the U.S. MEC. For complete guidance, see: https://www.cdc.gov/reproductivehealth/contraception/contraception_guidance.htm. Most contraceptive methods do not protect against sexually transmitted diseases (STDs). Consistent and correct use of the male latex condomreduces the risk of STDs and HIV.

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Fig. 15.1 (continued)

exams and tests need to be done? When the method should be initiated? How should common adverse events be managed? Both of these resources are downloadable in a free searchable app available at: https://www.cdc.gov/mmwr/volumes/65/rr/rr6504a1.htm for use in real-time when you are seeing a patient. Excellent companion documents have been published to explain the evidence underlying current recommendations [15].

Each woman should also be evaluated for her potential needs for protection from sexually transmitted infection and for emergency contraception (EC). Barrier methods should always be encouraged (as dual methods) to reduce the STD infection in at-risk couples. Advance prescriptions of levonorgestrel EC or ulipristal acetate EC should be offered routinely to all sexually active women who are not seeking pregnancy. Possible exceptions could be women using IUDs or implants, but each of the other methods has potential for non-use or incorrect use for which EC could provide back-up insurance. LNG EC can be combined with any other method, but it may not work as well in women with higher BMIs (see Section "Obesity"). UPA EC may not work as well if the woman has residual progestin in her system or if she restarts a progestin-containing contraceptive method before all the sperm have died (about 5 days after unprotected intercourse).

Guidelines for Women with Specific Medical Conditions

In this chapter, we will consider for each of the more common or potentially more serious medical conditions, the impacts that each medical condition may have on a woman's pregnancy outcomes, the impacts that each of the major reversible contraceptive options requiring prescription will have on her medical condition, and any drug-to-drug interactions that may be particularly important. While this chapter focuses primarily on reversible contraceptive options that require prescriptions, it is important to remember that couples who have completed their families have the additional options in permanent contraception. Vasectomy is clearly the very safest and most effective option of women with chronic medical conditions. Permanent contraceptive options for women generally entail slightly higher risks associated with anesthesia complications.

Some female barrier methods now require prescription (diaphragm, cervical caps, and perhaps vaginal gels for pregnancy prevention), but they are not discussed in this chapter because medical conditions usually do not play a role in identifying eligible candidates for these methods, except for the risks posed by their higher failure rates. Barrier methods should always be encouraged to reduce STD infection in at-risk couples.

Hopefully, couples are educated about methods they can use on their own (coitus interruptus, fertility awareness methods, external condoms, or spermicides) in case they do not have immediate access to other methods.

Diabetes

Diabetes affects more than 30 million women in the United States, 25% of whom are unaware of their diagnosis. Even among reproductive age women, 300,000 may have undiagnosed diabetes and an additional 2.5–7 million may be at risk [16]. Pre-existing diabetes complicates 0.9% of US pregnancies; gestational diabetes affects an additional 6% [17].

Diabetes, either Type I or Type II, can have devastating impacts on pregnancy. Pregestational diabetes is associated with significantly increased risks of congenital malformations, such as fetal cardiac anomalies and neural tube defects (especially caudal regression syndrome) [18]. To minimize birth defects, tight glycemic control should be achieved before conception with fasting glucose levels less than 100 mg/dL, 2-h post-prandial levels less than 120 mg/dL and hemoglobin A1C levels below 6.5% [19]. In addition to congenital malformations, Type I diabetes is associated with significantly increased risks for intrauterine growth restriction, preeclampsia, oligohydramnios, poor placentation, abortion, stillbirth, and perinatal death, while Type II diabetes is more likely to be complicated by macrosomia, polyhydramnios, stillbirth, preeclampsia, and birth trauma. Comorbidities add even more risks. Long term, the exposure to hyperglycemia in utero induces fetal programming that puts the offspring at risk for metabolic disease later in life [20]. Women with diabetes are often placed on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blockers for renal protection and statins for cardiovascular disease risk reduction. These agents are known teratogens that pose significant harm to the developing fetus especially early in pregnancy and are best stopped prior to conception; women should be switched to other medications associated with less fetal harm.

Preconceptional care has been shown to significantly improve most of the serious pregnancy challenges for both the diabetic mother and her fetus [21]. Contraception is key to that success, so efficacy and convenience are important features to consider; often IUDs and implants are considered first-line therapies for women who currently do not desire fertility [22, 23].

Which methods are appropriate to offer a woman with diabetes depends in large part on whether or not she has vascular disease, end organ damage, and, to a lesser extent, on the impact the method may have on her insulin sensitivity and glucose tolerance.

With a history of gestational diabetes that resolved postpartum, all methods are rated Category 1. For women with ongoing uncomplicated diabetes, even those requiring insulin, the copper IUD is Category 1; previous concerns about infections or reduced effectiveness of the copper IUD in women with diabetes have been resolved by clinical trials. Studies of progestin-only pills, progestin implants, and the LNG IUDs in women with all degrees of diabetes have found that these methods have no clinically significant adverse impacts on glycemic measures or lipid profiles, so they are rated Category 2 [24–28]. However, women using DMPA demonstrated increases in fasting glucose and LDL cholesterol as well as decreases in HDL cholesterol, although no significant dose changes were needed in their treatment with insulin or oral hypoglycemics [29].

Even women with diabetes that is long-standing (>20-year duration) or that is complicated by neuropathy or retinopathy can still use most progestin-only methods because the benefits generally outweigh the risks (Category 2).

The only exception is the Category 3 rating for DMPA. DMPA use in women with complicated or long-standing diabetes is considered less favorably because of the metabolic changes noted above (in both carbohydrate and lipid metabolism), hypoestrogenism, and potential weight gain associated with its use.

Contraceptive progestins offer noncontraceptive health benefits. For example, they can help reduce the *increased* risk of Type I endometrial cancer that women with diabetes face [30]. They also reduce excessive menstrual blood loss associated with anovulatory cycling, which is more commonly seen in women with Type II diabetes.

Estrogen-containing hormonal contraceptives traditionally have been used with extreme caution in women with diabetes because of concerns about their adverse impacts on insulin sensitivity and glucose tolerance. However, diabetic women using modern low-dose formulations of pills and the contraceptive vaginal ring have shown no differences in hemoglobin A1C levels when compared to copper IUDs users [27, 31]. Conflicting results have been seen in studies that have used as outcomes the changes in insulin dosing needed to maintain fasting glucose levels [24, 27, 29, 32]. For women with complicated diabetes, estrogen-containing methods are Category 3 or 4; they are generally to be avoided because of presumed presence of severe microvascular disease in those women, which will predispose them to venous and arterial thrombosis. The common presence of significant comorbidities, such as obesity, hypertension, and dyslipidemia, also weighs against use of combination methods for those women.

Hypertension

Cardiovascular diseases (CVD) combined account for over a third of maternal deaths in the United States [1]. Hypertension is the most common type of CVD during the reproductive years.

Like diabetes, hypertension is frequently underdiagnosed and, in pregnancy, poses significant risks to both the woman and the fetus. In addition, teratogenic medications are often used to treat hypertension. Endothelial damage inflicted by chronic hypertension alone raises maternal risks for myocardial infarction, stroke, superimposed pre-eclampsia, and eclampsia. For the fetus, maternal hypertension can result in placental insufficiency, intrauterine growth restriction, placental abruption, and perinatal death [33]. Again, contraception is key to optimize pregnancy outcomes by providing time for the women prepare for pregnancy. Switches can be made in antihypertension medications from teratogenic therapies such as ACE inhibitors and selective receptor blocking agents to medications that have established safety records in pregnancy, such as hydralazine, labetalol, or nifedipine.

Not all forms of contraception are appropriate for use in the face of hypertension; some can increase the risk of hypertension itself as well as the risks of hypertensive complications. One clear exception is the copper IUD. Regardless of the severity of the blood pressure or the presence of any hypertensive complications, copper IUDs are rated Category 1.

Although it is not known if adequately controlled hypertension poses any greater risks than blood pressure of up to 159/99, eligibility criteria ratings are the same for that level of untreated hypertension and adequately controlled disease. Estrogen-containing methods are generally to be avoided (Category 3, 4) because of their thrombotic potential as well as direct impact on vasoconstriction, but progestin-only methods are more acceptable. In WHO studies, composite cardiovascular disease events (stroke, venous thromboembolism, and acute myocardial infarction) in hypertensive women who used progestin-only methods were elevated but overlapped the prevalence rates for those events of hypertensive non-users [34].

Therefore, progestin-only methods with the exception of the injection are also Category 1 options for women with isolated mild hypertension but are Category 2 for higher blood pressure categories and hypertension with known vascular disease.

DMPA, perhaps because of its potential adverse lipid impacts and possible association with weight gain, is rated Category 2.

The recommendations listed above apply to women who have mild hypertension with no other risks for cardiovascular disease, such as dyslipidemia, older age, heavy smoking. For women with hypertension and any of those other risk factors for CVD, the recommendations are the same as women with more severe hypertension. For more severe hypertension (systematic BP ≥ 160, diastolic BP ≥ 100) and for hypertension complicated by vascular disease, combined hormonal contraceptives are not acceptable (Category 4); the progestin-only implants, intrauterine devices, and pills are Category 2; and the injection is Category 3. Age is a particularly important independent risk factor for hypertensive complications. The risk of cardiovascular disease with use of estrogen-containing pills by hypertensive women in their 40s is almost four times higher than it is in hypertensive women in their 20s [35].

In studies that ranged from 6 months to over 8 years, estrogen-containing methods used by healthy women raised both systolic and diastolic measurements only modestly from 3 to 9 mmHg [36, 37]. However, in women with hypertension, estrogen-containing contraceptives significantly raise the risks of hemorrhagic and ischemic stroke and myocardial infarction [38]. In developed countries, the risk of acute myocardial infarction was increased nearly 10-fold with use of combined oral contraceptives by women with hypertension [39]. The risk of hemorrhagic stroke was only slightly elevated (<2-fold), but the risk of ischemic stroke almost tripled by adding COC use to essential hypertension [40].

Migraine Headaches

Migraine is a recurrent, debilitating, neurological condition that afflicts 17% of US adults and disproportionately affects women (3:1 ratio) [41]. Worldwide, migraine headaches are the seventh leading cause of time spent disabled [42]. About 5% of women have migraine with aura. Migraine prevalence is highest during reproductive years when 22–37% of women will experience at least one episode. As many as 4% of women suffer migraine headaches more frequently than 15 days a month [43].

> Migraines (especially migraine headaches with aura) are associated with a doubling of the probability for ischemic stroke. The presence of other risk factors, such as smoking cigarettes, hypertension, diabetes, and ischemic heart disease, greatly magnifies that peril; higher frequency of migraine headache also increases the likelihood of such strokes [44].

It is important to distinguish migraine headaches from other types of headaches, since all non-migraine headaches—regardless of severity—are rated Category 1 for all methods of contraception. Women often use the word “migraine” to describe very intense, painful headaches. Longer duration of pain (4–72 hours), temporal location, and unilaterality of the pain are far more common features of migraines.

The characteristics of the pain—throbbing, pounding that is exacerbated by routine movement—also helps identify migraine in contrast to other headaches. Finally, the presence of other complaints, such as nausea, vomiting, neck pain, and sensitivity to light or sound, support the diagnosis.

Having identified a headache as migraine, it is also important to assess if it is accompanied by aura. By definition, aura should be diagnosed in cases when the patient has had at least two episodes with symptoms that lasted 5–60 minutes and developed gradually over at least 5 minutes and where onset preceded the headache but by no more than 60 minutes. Relevant symptoms include reversible abnormal vision (wavy lines, bright, or dark spots), abnormal speech (language dysfunction), and/or sensory symptoms (numbness, tingling, vertigo) [45]. Tools such as the Visual Aura Ratings Scale can be helpful in diagnosing aura [46].

Current consensus recommendations for women with migraines without aura permit unrestricted use of all progestin-only methods and nonhormonal methods (Category 1). Estrogen-containing methods are Category 2, for women under age 35, but women should be carefully screened for other risk factors associated with stroke before combined hormonal methods are offered [47].

For women with migraine headaches with aura, all progestin-only and nonhormonal methods are allowed without restriction, but all estrogen-containing methods must be avoided [47]. Similar recommendations are made by some expert panels for women who have migraine without aura as well as other cardiovascular risk factors (cigarette smoking, hypertension, obesity) [47]. Studies show that combined hormonal contraceptives with <50 mcg ethinyl estradiol or estradiol valerate increase the risk of ischemic stroke by two- to sixfold in women with migraines with aura, raising the risk from 5.9 to 36.9/100,000 women [47]. Data on younger women who use low dose formulations is not robust [41]. The International Headache Society suggests that in the absence of other risk factors for stroke, low dose pills may be permitted in young women with aura because the absolute risk for stroke is so low [44], but that recommendation has not been endorsed by all US experts.

Anticonvulsants, such as valproic acid and topiramate, are sometimes used to treat migraine headaches. These medications are teratogenic and should be avoided in women at risk for pregnancy [48]. The efficacy of the contraceptive method is especially important when some anticonvulsants are employed. Some anticonvulsants increase hepatic metabolism of sex steroids and may reduce the effectiveness of low dose systemic hormonal contraceptives (see below).

Menstrual migraine that is not associated with other migraines or with aura is analyzed in a separate category within the US MEC. The symptoms of menstrual migraine result from a drop in circulating estrogen levels that accompanies

involution of the corpus luteum cyst at the end of the cycle. Therapies that suppress estrogen fluctuations (DMPA and perhaps POPs) may control symptoms. Shortened hormone-free intervals in combined oral contraceptive formulations alone or when used with estrogen supplementation during the hormone-free pill days can also help reduce symptoms. Extended cycle (continuous) use of oral pills or rings is especially effective in controlling fertility, bleeding, and menstrual migraine headache [49].

Seizure Disorders

Practice guidelines for the women with seizure disorders advise women to achieve optimal seizure control with the minimum effective dose of antiepileptic drugs (AEDs) and to take recommended dose of folic acid (FA) supplement prior to conception [50]. Despite this clear guidance, recent cross-sectional data from an online survey of reproductive-age women with epilepsy found that 44.6% of at-risk women used systemic hormonal methods, but 7% in that group used AEDs which reduced the efficacy of their method; 30.6% used IUDs; 23.1% used only barrier methods; 2.2% used no method. Only half of women used folic acid supplements; non-consumption of folic acid used was not related to the effectiveness of the method used [50].

Many of the AEDs are teratogens. Valproic acid is associated with eight specific types of major congenital malformations. The risk of spina bifida is nearly 20 times higher in women using valproic acid than it is in women not using the drug [51]. Phenobarbital and Dilantin increase the risks for cleft lip, microcephaly, digital abnormalities, and low set ears. Topiramate increases the risk of cleft lip nearly sevenfold [51].

> Hormonal contraceptives do not affect seizure frequency directly but may act indirectly by impacting seizure therapy. Progestins raise seizure thresholds and estrogens lower them. Depo-medroxyprogesterone use may decrease seizure frequency and will not impact seizure therapy.

Fortunately, all combined hormonal methods are progestin dominant. However, many AEDs increase hepatic metabolism of sex steroids via the cytochrome P450CY3 pathway, thus lowering circulating levels of the contraceptive and increasing risk of unintended pregnancy [52] (see Table 15.1). Carbamazepine is particularly notable; it reduces circulating levels of ethinyl estradiol, norethindrone, and levonorgestrel by 50% [53]. On the other hand, it must be remembered that estrogen increases the metabolic clearance of many AEDs, so AED dosing may need to be adjusted. The locally acting IUDs are rated Category 1. All systemic hormonal

Table 15.1 Antiepileptic agents' impact on metabolism of hormonal contraceptive agents [46]

AEDs that induce Sex steroid metabolism	AEDs that do not induce Sex steroid metabolism
Carbamazepine	Acetazolamide
Eslicarbazepine	Clonazepam
Felbamate	Ethosuximide
Oxcarbazepine	Gabapentin
Perampanel	Lacosamide
Phenobarbital	Levetiracetam
Rufinamide	Pregabalin
Topiramate (higher dose)	Tiagabine
	Vigabatrin
	Zonisamide

methods are rated Category 1 for safety, but only the injection is resistant to the increased hepatic metabolism when used with certain AEDs.

> NB: Lamotrigine and valproic acid do not affect metabolism of sex steroids but do often need changes in their dosing because estrogen affects their hepatic clearance

Some of the older AEDs (Dilantin and phenobarbital) decrease hepatic vitamin K synthesis, which results in heavier menstrual bleeding. These agents can also be used to treat depression or substance abuse; it is important to remember these drug-drug interactions for all clinical applications. Hormonal contraceptive methods can help reduce this excessive blood loss and improve the quality of life [54].

Coagulation Disorders

Hypercoagulative Conditions

Several conditions such as prior venous thromboembolism (VTE), systemic lupus erythematosus (SLE), sickle cell anemia, major surgery with prolonged immobilization, and gene mutations (including mutations in Factor V_{Leiden} and prothrombin and alterations in protein S, protein C and antithrombin III) substantially increase risk of venous and arterial thromboembolism (VTE) and ATE.

> Screening for inherited thrombophilia prior to starting estrogen-containing methods is not indicated because the risk is so very low; over 90,000 women with Factor V_{Leiden} mutation would need to avoid CHC use to prevent 1 VTE-related death [55].

Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disorder that can affect multiple organ systems.

In pregnancy, SLE increases risks for ischemic heart disease, stroke, and venous thromboembolism, SLE flares, superimposed preeclampsia, intrauterine growth restriction, and pregnancy loss especially if the disease has been active in the prior 6–12 months. Both arterial thromboembolism and venous thromboembolism risks are significantly increased if the woman has antiphospholipid antibodies (lupus anticoagulant, anti-beta 2 glycoproteins, or anti-cardiolipin).

Women without antiphospholipid antibodies (with or without immunosuppressive therapy) are rated as Category 2 candidates for all hormonal contraceptives.

The Category 2 rating reflects prior studies that suggested increased risk of thromboembolism [56]. Copper IUDs are Category 2 for those on immunosuppressive therapy due to the possible risk of infection with IUD placement. However, the copper IUD is Category 1 for the rest of women with SLE with normal platelet counts, whether or not they have antiphospholipid antibodies. Due to concerns about thrombosis, for women with SLE with known or unknown antiphospholipid antibodies, progestin-only methods are rated Category 3 and all estrogen-containing methods are rated Category 4.

Deep Venous Thrombosis/Pulmonary Embolism

Pregnancy and the postpartum periods are hypercoagulative times that pose risks of venous thromboembolism greater than associated with any contraceptive method. However, because contraception is used by otherwise healthy women, method choice depends on the woman's risks for clotting.

For women with a family history of affected first-degree relatives, but no personal history of VTE, all non-hormonal and progestin-only methods are Category 1; estrogen-containing methods are considered generally acceptable but are rated Category 2. For women with an acute episode of thrombosis (deep venous thrombosis or pulmonary embolism), *all* methods are Category 2, except estrogen-containing ones, which are unacceptable (Category 4).

Prior personal experience with thromboembolism predisposes to recurrence. All appropriate actions should be taken to help avoid pregnancy until the woman is prepared. For women with known thrombogenic mutations, as those with prior DVT or pulmonary embolism not receiving anticoagulation, copper IUDs are Category 1; all progestin-only methods are generally acceptable (Category 2), but estrogen-containing methods are not (Category 4). CHCs may be Category 3 for women with personal history of DVT/PE with low risk of recurrence. Anticipated major surgery by itself significantly impacts estrogen-containing methods, which are generally to be avoided (Category 4 prolonged immobility or Category 3 if no such immobilization is anticipated). Minor surgery without immobilization does not limit choices. Recommendations for women receiving anticoagulants are covered in the following section. Women with history of superficial thrombosis are eligible for all non-estrogen-containing methods (Category 1), but estrogen-containing methods are Category 3.

Compromised Coagulation States

Women who are medically anticoagulated and those with genetic or acquired disorders that impair blood clot formation and/or clot maintenance (thrombocytopenia, von Willebrand disease, excessive fibrinolysis) usually experience significant heavy menstrual bleeding and hemorrhagic complications with pregnancy.

In general, the copper IUD may be useful (Category 2) if the woman can tolerate 30–55% increase in blood loss. Methods that reduce blood loss are rated similarly (Category 2) but may be favored if the woman suffers heavy menstrual blood loss.

For women who are therapeutically anticoagulated, many more complicated issues are raised. Often the drugs (i.e., Coumadin) are teratogenic, so method efficacy is critical; pregnancy should be delayed until anticoagulation medication can be switched.

Ovulation suppression is important for all women with coagulation defects because extrusion of the oocyte from the follicle can cause internal hemorrhage. Hormonal IUDs are excellent for contraception and bleeding, but do not reliably suppress ovulation.

Implants provide contraception and ovulation suppression but have lower levels of amenorrhea. Injections generally can achieve all three objectives, especially if the woman has frequent contact with the medical system and is less likely to miss reinjections. To prevent hematoma with intramuscular injection, direct pressure (not massage) needs to be applied to the injection site for 5–10 minutes following administration; the subcutaneous formulation of DMPA may be preferred.

Estrogen-containing products are Category 4 for anticoagulated women at high risk for VTE recurrence and Category 3 for those at low risk. Continuous, extended cycle use of pills or vaginal rings should be encouraged to reduce bleeding and escape ovulation. Seven-day placebo formulations of low-dose pills should be replaced by formulations with no more than four placebo pills. For women with severe thrombocytopenia with SLE, recommendations are slightly different. Initiation of copper IUDs or DMPA is Category 3, but continuation is Category 2. All other methods are rated Category 2.

Anemias

None of the anemias (thalassemia, sickle cell anemia, or iron-deficient anemia) raises any significant concerns for the use of any of the prescription methods.

The copper IUD is Category 2 for anemia because it generally increases blood loss by 30–55% [57]. Sickle cell anemia warrants more specific attention since it is characterized by long-term organ infarction and, in pregnancy, with increased risk of fetal demise, intrauterine growth restriction, preterm birth, hypertensive disease, and maternal mortality. Estrogen-containing methods are classified Category 2 for women with sickle cell anemia due to remaining concerns about VTE risk. Progestin-only methods, which are rated Category 1, offer important noncontraceptive advantages. They limit menstrual blood loss. Injectable progestins also reduce the frequency of acute sickle cell crises by 70% and reduce the severity of the remaining crises; combined oral contraceptive use also reduces incidence of acute sickle crises by 50% [58].

Outside of the US MEC recommendations, clinicians should remember that severe anemia from any cause is often associated with thrombocytosis, which greatly increases VTE risks. At a minimum, be sure to check platelet counts before offering estrogen-containing medications to women with chronic anemia [59].

Mental Health Disorders

Mental health problems afflict substantial numbers of reproductive-age women in the United States. The NHANES survey found that 3.8% of those women reported current major depression and another 4.3% suffered minor depression [60]. A woman's lifetime risk for depression is over 22%; anxiety disorder similarly affects 1 in 5 women [61]. Bipolar disease, schizophrenia, post-traumatic stress disorder, and eating disorders also are commonly found among women at-risk for pregnancy. In addition, mood disorders present as part of PMS and PMDD for countless women each month.

Depression has serious consequences in pregnancy. Suicide is a leading major cause of maternal mortality [62]. Risks of preterm births, low birthweight, and intrauterine growth restriction are increased with depression [63]. Postpartum depression risks are dramatically increased in women with pregestational depression. There is widespread belief among the general public, amplified by the media, that hormonal contraceptives (particularly progestins) may precipitate or exacerbate symptoms [64]. In part this may be attributable to the fact that women report mood swings due to hormonal fluctuations and many women suffer catamenial worsening of their disorders, but this is due to *loss* of hormonal support not to increased exposure [65]. Biological justification has been claimed because women using older, higher dose combined hormonal methods have been found to have lower circulating levels of pyridoxine even though all those levels were still well within normal limit [66].

A systematic review concluded that use of oral contraceptives, hormonal IUDs, or DMPA by women with depressive or bipolar disorders was *not* associated with worse clinical course of disease compared to no hormonal use [67]. As the method with the highest levels of progestin and the most profound impact on ovarian steroid production, it would be expected that DMPA would pose the greatest risks for mood disorders. However, a multicenter prospective study of 495 women who were formally evaluated for depression prior to initiation of DMPA and at 1 year found that depressive scores dipped over time; those with the highest baseline scores also improved [68].

The US MEC only evaluates the eligibility of women with depressive disorders; each of the prescription methods is rated Category 1 with an asterisk to remind clinicians to evaluate the other drugs that the woman may be using to control her depressive symptoms. Many psychotropic agents as well as St. John's Wort are potent inducers of cytochrome P450 enzymes that may reduce the efficacy of all systemic hormonal therapies, with the possible exception of injectables. While not a medical contraindication, it should be noted that in women, low self-esteem and depressive symptoms are related to ineffective use of contraceptives [69].

Since the publication of the US MEC, two studies have linked depression to progestin-containing methods and two others have been more reassuring. One large population-based study recently reported higher rates of first depression diagnosis (and treatment) in users of progestin-only methods. However, the retrospective nature of this study and the lack of validated measurements as well as an inverse dose-effect significantly undermined the strength of these findings [70]. A second prospective population survey compared self-reports of depressive symptoms (DSM-IV) of COC users to nonusers as they aged from 11 to completion of the study at age 25. Overall depression rates did not differ between the groups, except at age 16 when the COC users had higher rates of depressive disorders (OR < 2.0). The limitations of this finding was that at age 16, COC users had higher prevalence of risk factors for depression than nonusers; they had lower SES, were more likely to be foreign, and were more likely to have been sexually active at the time of COC

use [71]. Balancing these two studies that received much more media attention were two more comprehensive reviews. One was a survey of thousands of adolescent pill users that showed no association with use of oral contraceptives and lifetime risk of depression or current depressive disorders [72]. The second was an earlier review of 46 studies which showed most CHC users had a beneficial effect or no effect on mood symptoms [73].

Based on the preponderance of the data, there is no compelling data linking hormonal contraceptive use to depressive scores or to the diagnosis of depression for the general population of users. Undoubtedly, there may be individual differences in hormone absorption and metabolism as well as in sensitivity to hormones [74]. However, the most important variable is patient expectation, which can be influenced by counseling. Telling a woman about a potential "nocebo side effect" markedly increases the probability that she will experience that adverse event and has raised ethical issues about including warnings about these effects in the discussion with potential users [75]. Therefore, if reassurance does not convince the woman who raised the concern, it may be prudent to suggest nonhormonal alternatives.

For women with catamenial worsening of psychiatric symptoms, elimination of scheduled bleeding episodes and, more importantly, elimination of hormonal fluctuations of the menstrual cycle may offer important noncontraceptive benefits to the woman and to her family.

The low dose drospirenone 24/4 formulation of combined oral contraception is as effective in treating the entire spectrum of PMDD symptoms as other FDA-approved agents such as SSRIs [76].

Functional hypothalamic amenorrhea (FHA) often results from extreme stress and is associated with eating disorders, excessive exercise, and osteoporosis (the athletic triad), as well as dyslipidemia. While hypoestrogenism is the common endocrinopathy, current recommendations are that hormone replacement (with combined hormonal contraceptives) should *not* be used as first-line therapy. CHCs are not contraindicated if the woman needs contraceptive protection, but she should be advised that the scheduled bleeding she will experience with their use does not represent cure [77].

A related concern is the safety and effectiveness of hormonal methods for women with opioid use disorder. Rates of unintended pregnancy in this group can be as high as 86% [78]. Utilization of contraceptives by women with substance use disorders is very low – only about half use any method [79]. Addiction during pregnancy carries many risks including restricted fetal growth, placental abruption, preterm labor, fetal demise, and neonatal abstinence syndrome [80].

A recent literature review found no direct research addressing these issues, but experts have examined theoretic concerns and found no basis to limit use of any of the methods in women without comorbidities that would otherwise preclude method use.

Also, they found no drug-drug interactions that would reduce method effectiveness. Correct and consistent method use may be compromised by recreational drug use, but many users are high-functioning and capable of contracepting successfully. However, it should be noted that estrogen may be a weak inhibitor of hepatic isoenzymes responsible for opioid clearance, which could lead to toxicity and perhaps overdose [81].

Obesity

As widespread a problem as obesity is today, the latest predictions are that within a decade nearly half of US adult women will have body mass index greater than 30 kg/m^2 and the most rapidly growing weight group will be the "extremely obese" [82]. Obesity is the fifth leading cause of mortality worldwide [83]. Obesity reduces fertility [84], but when pregnancies do occur, they are complicated by greater risk for miscarriages, major congenital malformations, gestational diabetes, preeclampsia syndrome, preterm birth, low Apgar scores, and stillbirth [85, 86].

> Although substantial numbers of clinicians have misconceptions about the safety of IUDs for women with high BMIs, the US MEC rates all non-estrogen-containing methods as Category 1 [87].

Efficacy for locally acting IUDs as well as systemically acting implant and injections is not affected by obesity [83]. Estrogen-containing methods are rated Category 2, reflecting concern for risk of venous thromboembolism. Other risk factors for VTE, cardiovascular disease, and stroke, such as immobility, tobacco use, hypertension, dyslipidemia, and family history, should be considered when offering combined hormonal methods to women with high BMIs.

Beyond the possible medical contraindications, there is debate about the question, "do orally administered hormonal contraceptive have higher failure rates for obese women?" [88] Certainly, women who have undergone bariatric surgery (Roux-en-Y procedures) that diminish gastrointestinal absorption would be better served by non-oral routes of administration. Beyond that, pharmacokinetic evidence supports lower efficacy of CHCs when used by women with higher BMIs. Studies have demonstrated slower absorption of progestins, lower peak levels, and larger volumes of distribution in obese subjects [89]. Obese women required double the dose of LNG-EC pills to achieve the Cmax levels that normal weighted women reached with a single dose [90, 91]. Failure rates with the contraceptive patches and the new vaginal contraceptive ring were highest among women with weight greater than 90 kg or with BMIs greater than 30 kg/m^2 [92, 93].

Other investigators have demonstrated that inconsistent hormonal contraceptive use is far more common among women with high BMIs [94]. Since obesity is more common among women in the lower SES groups, issues of ongoing method access

and other medical and real-life issues may compromise successful contraceptive use by obese women. Issues of mistrust with the medical system may also influence use and should motivate clinicians to assure that all possible biases have been rooted out and that patient-centered care is provided.

HIV-AIDs

In developed countries, antiretroviral therapy has been so successful in reducing viral load that individual cases of complete cure have been reported. Although the rate of new HIV diagnoses declined from 2013 to 2017, that rate increased for people aged 15–34, with the highest rates among 25–29-year-olds [95]. A larger challenge is that approximately 1 in 7 HIV-infected individuals in the United States remains undiagnosed. Globally, the burden of the disease and unwanted pregnancy are even greater. Dual method use at the time is the best approach to reduce both risks [96]. While safer sex practices and PrEP are at the core of all STD prevention programs, HIV infection brings forth questions about the impact a method might have on infection and about possible drug-drug interactions. Comorbidities often influence decision-making.

> For women at high risk for HIV infection implants, progestin-only pills and combined hormonal contraception are rated Category 1. IUDs and injections are rated Category 2.

Spermicides with nonoxynol-9 do not protect against HIV infection and may even increase the risk of HIV transmission if used frequently. Therefore, spermicides alone or when used with other methods are not advised for women at high risk for HIV infection. The safety of DMPA had been questioned for at-risk women because early observational studies reported an increased rate of seroconversion among DMPA users [97].

However, the ECHO study, an 18-month randomized open-label trial conducted in 12 sub-Saharan countries with high HIV prevalence, found no statistically significant differences in HIV acquisition rates among users of the LNG implant, DMPA, and copper IUDs. The study was powered to detect a 50% difference in infection rates between methods [98]. Despite this reassuring finding, some experts encourage use of NET-EN injections (where available) in lieu of DMPA because of potential lower rates of HIV acquisition rates [99].

Although use of prescription contraceptives remains low among HIV-infected women, for those who are clinically well and receiving antiretroviral therapy, IUDs are Category 1 and all systemic hormonal therapies are rated Category 1 except as modified by drug-drug interactions with antiretroviral (ARV) therapies [100]. Fosamprenavir use converts estrogen-containing methods to Category 3 and all other systemic hormonal methods to Category 2. All other AVRs still leave those

hormonal methods as Category 1 or 2. For HIV-infected women who are not clinically well or not on medication, initiation of IUDs becomes Category 2, but all other contraceptive methods are still Category 1.

Physical or Intellectual Disabilities

Although not explicitly covered in the US MEC, it is important to recognize that one in ten women of reproductive age has a disability [101]. Based in common activity limitations, there are categories of physical disabilities (cerebral palsy and spinal cord injuries), sensory disabilities (vision and hearing), and intellectual and developmental disabilities (Down syndrome, fetal alcohol syndrome) [101]. Increasingly women with these disorders are becoming pregnant and face greater risks of maternal and fetal complications. In general, contraceptive concerns for those with limitations on physical activity revolve around their higher risk for thrombosis. In some cases, menses may present hygiene challenges. Those with visual compromise may benefit from longer acting methods for convenience, but certainly have no medical contraindications to any method.

For those with intellectual and developmental disabilities, issues of informed consent are important; but other issues such as menstrual problems (hygiene and catamenial symptom worsening), vulnerability to sexual assault and intrinsic sexual drives require consideration [102].

There is concern that the higher rates of permanent contraception and hysterectomy and the early age at which these procedures are performed may represent coercion and a remnant of historical practices intended to control marginal minorities [103]. It is important to recognize that while such procedures should still be considered viable options on an individual basis, care must be taken to insure that patient preferences are respected.

Studies have found that injectable contraception is frequently used by women with intellectual and developmental and physical disabilities but IUDs and implants are not. This may reflect lack of access or clinician ability to offer more effective methods in a typical office visit [104]. A recent survey found that 44.7% of gynecologic practices were inaccessible to women with physical disabilities [105]. Equipment and policies to provide sedation during contraceptive placement may be even more rare.

Gynecologic Cancers

Women with gynecologic cancers are at high risk for complications with pregnancy and worsening of their conditions in the absence of treatment during pregnancy. Some gynecologic cancers are hormonally responsive and, therefore, hormonal

methods are not recommended in these patients. The Society of Family Planning has published clinical guidelines for contraception in women with cancer that serve as an excellent detailed resource [106].

Breast Cancer

Women with benign breast conditions and those with a family history of breast cancer are eligible (Category 1) for all methods of contraception. Undiagnosed breast masses not suspicious for carcinoma are rated Category 2 for all hormonal methods. In the summary of the US MEC there are no recommendations for known carriers of high-risk mutations (BRCA 1 or 2). There has been some reassuring research about COC safety in this population especially considering the role COCs have in reducing ovarian cancer risk [107]. Consensus is emerging that there is a temporary (reversible), relatively small increase in breast cancer risk associated with use of higher dose combined hormonal methods, approximately equivalent to the risk seen with pregnancy. The risk with lower dose formulations is not as clear [108].

Long-term follow-up has shown no increase in mortality from breast cancer in former users of combined hormonal contraceptives [109, 110].

For women within 5 years of diagnosis of breast cancer, only the copper IUD is Category 1; all hormonal methods are to be avoided (Category 4).

No distinction is made based on receptor status of the carcinoma. Even low dose exposure from LNG-IUS raises the possibility of higher recurrence rates with method continuation (versus removal) or with use for endometrial protection during tamoxifen therapy [111]. For women who are breast cancer free for at least 5 years, use of hormonal methods may be considered with caution (Category 3).

Endometrial and Cervical Premalignancies and Cancers

IUDs may decrease the risk of both endometrial and cervical carcinoma [112].

All methods are rated Category 1 for endometrial hyperplasia. In fact, the LNG IUS is the most effective medical therapy for endometrial hyperplasia [113]. However, the impact the copper IUD may have on menstrual blood loss may discourage its use until the hyperplasia has been resolved.

Case reports show that in select cases both endometrial hyperplasia with atypia and early-stage endometrial cancer may be successfully treated by experimental use of the higher dose LNG-IUS. These case generally involved young nulliparous women [114].

Cervical dysplasia is not a contraindication to the use of any method, although copper IUDs and POPs are rated Category 1 while all other methods are Category 2. Cervical cancer treatment usually removes the need for contraception, but while the woman is awaiting treatment, initiation of an IUD is not permitted, but continuation of IUDs is Category 2 as are all hormonal methods, except progestin-only pills (Category 1).

Ovarian Cancer

Combined hormonal contraceptive methods have long been known to reduce the risk for ovarian cancer [115, 116]. Newer studies have shown that use of intrauterine devices (hormonal or not) may also reduce that incidence [117].

All methods of birth control are rated Category 1 for use by women with history of ovarian cancer.

Conclusion

The above is by no means an exhaustive list of all medical conditions experienced by patients, but it represents an introduction to the literature and available resources on the subject. Although contraception is not risk free, it is considerably safer than unplanned and unprepared for pregnancy. Every clinician should make the US MEC easily accessible for use during patient visits. For women of reproductive age, this tool can be easily integrated into the reproductive life plan discussion, and more popular access to its finding can be found in the Bedsider.org app. Use of the US MEC and the companion Selected Practice Recommendations for Contraception can increase contraceptive safety and lead to a reduction of the rate of unplanned pregnancy among our most vulnerable patients.

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Chapter 16
Contraception for the Postpartum Period

Rachel B. Danis

Immediate Postpartum Contraception

Contraception in the postpartum period can be initiated immediately or in the outpatient setting [12, 13]. The immediate postpartum period can have many meanings [13, 14]. Immediate post-placental insertion of an intrauterine device (IUD) is defined by the first 10 minutes after delivery of the placenta. Immediate postpartum can also be defined as within 10 minutes of delivery of the placenta to 72 hours postpartum [12, 14].

Immediate postpartum contraception typically refers to using long-acting reversible contraception (LARC) methods, which includes IUDs and the etonogestrel implant. Benefits of immediate postpartum LARC insertion include its convenience, safety, and efficacy [4, 15]. There is no interference with breastfeeding, and the provider avoids performing an uncomfortable insertion in the outpatient setting at a later date. Immediate LARC initiation also improves postpartum contraceptive rates, which then reduces unintended pregnancy and short interpregnancy intervals [4, 15, 16]. The American College of Obstetricians and Gynecologists recommends providers and institutions to develop processes for stocking LARCs on labor and delivery units in order for IUDs and implants to be available as effective options for immediate postpartum contraception [17].

> It is important to note that inserting an IUD immediately after delivery of the placenta, regardless of mode of delivery, has not been associated with increased infection, uterine perforation, or postpartum bleeding [4].

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One disadvantage of immediate IUD insertion is the potentially higher risk of expulsion when compared to delayed insertion at the postpartum visit. However, this increased risk should not preclude immediate insertion but rather be incorporated into one's contraception counseling [14, 16]. Sonalkar and Kapp conducted systematic review to assess expulsion rates with postpartum LARC insertion (both levonorgestrel [LNG]- and copper-containing IUDs) in both vaginal and cesarean deliveries at various postpartum time points [13]. When comparing post-placental IUD (LNG or copper, manually or with ring forceps) insertion versus insertion between 10 minutes and 48 hours of delivery, one randomized control trial (RCT) showed similar expulsion rates between the two groups [18]. Three cohort studies investigating this issue of timing showed similar safety, similar number of post-insertion bleeding days, and no clinically evidence cases of perforations in both groups [13, 19–21]. Two of these studies reported similar expulsion rates [20, 21], but the study by Chi et al. demonstrated a higher rate of expulsion in the >10-minute to 48-hour group compared to the <10-minute group ($p < 0.001$) [13, 19].

Studies comparing outcomes in immediate, <10 minutes, insertion versus 10 minutes to 72 hours postpartum are fair to poor quality, and data widely varies [13]. One study reported an expulsion rate of 70% in the 10-minute to 72-hour group [22], while another reported an expulsion rate of 5% in this group [23]. These studies included both vaginal and cesarean deliveries but only included cases with the copper-IUD[22,23]. Two RCTs evaluating expulsion rates of LNG-IUD with post-placental insertion versus insertion at the 4–6weeks postpartum visit showed expulsion rates in favor of the delayed insertion at the postpartum visit [13, 18, 24]. Interestingly, data from these RCTs showed that due to the high follow-up and available funding for replacements of expelled IUDs, IUD use at 6 months postpartum is similar in both groups [13].

In summary, expulsion rates with immediate postpartum contraception favor insertion within 10 minutes from delivery versus 10 minutes to 72 hours postpartum [13]. However, expulsion rates with immediate insertion are still higher than the expulsion rates in women initiating an IUD at the postpartum visit, 4–6 weeks after delivery [25, 26]. More data are needed to compare expulsion rates between LNG- and copper-containing IUDs [13]. LNG-containing and copper-containing IUDs are highly ranked according to the US MEC criteria, and both should be incorporated into one's contraceptive counseling [12].

Postpartum Contraception for the Breastfeeding Mother

The American Academy of Pediatrics Policy Statement on breastfeeding reports significant health benefits for both mother and baby [27]. Patients and providers may assume that hormonal contraception carries inhibitory effects on lactation, but breastfeeding should not deter a woman from utilizing contraception in the

postpartum period [4, 12, 28, 29]. Ideally, the contraceptive method used in breastfeeding women augments rather than diminishes lactation [30].

Immediate Postpartum LARC Contraception and Breastfeeding

Progesterone is rapidly cleared following delivery of the placenta, and it is this drop in progesterone that triggers lactogenesis [26, 31]. If this decline is interfered by a progestin-containing contraception, there is concern that lactogenesis could be impaired [4, 26, 31].

> However, no reduction in breastfeeding has been observed in randomized controlled trials involving either early or immediate post-placental LARC insertion [4, 28].

Gurtcheff et al. randomized women ($n = 69$) who desired the etonogestrel implant to have the insertion 1–3 days postpartum or 4–8 weeks postpartum [28]. There were no statistically significant differences in demographics, mode of delivery, use of anesthesia, or prior breastfeeding history in either group. Early insertion proved to be non-inferior to the 4–8 weeks postpartum insertion as far as time to lactogenesis and incidence of lactation failure [28].

A systematic review of 26 studies examining postpartum LNG-IUD use showed that the LNG-IUD had no effect on milk production or on infant growth and can safely be used in both the immediate postpartum and 4–6 weeks postpartum period in lactating women [30]. Turok et al. examined this relationship by randomizing 285 women who both desired to breastfeed and to receive a LNG-IUD postpartum to receive either immediate IUD insertion or delayed insertion at the postpartum visit [26]. Analysis showed that there was no difference in the prevalence of breastfeeding at 8 weeks postpartum, nor was there a difference in time to lactogenesis between groups [26].

The US MEC states that breastfeeding women using IUDs do not have increased risk for certain IUD-associated adverse events including expulsion, infection, pain, or bleeding compared to non-breastfeeding women. The copper-IUD is classified as category 1 (no restriction), and the progestin-containing LARCs (LNG-IUD and etonogestrel implant) are classified as category 2 (advantage of use generally outweighs risk) for breastfeeding women in the immediate postpartum period [12].

> In conclusion, breastfeeding is not a contraindication to immediate LARC insertion and should be considered an appropriate contraceptive option.

Non-immediate Postpartum LARC Contraception and Breastfeeding

Numerous studies have found the initiation of progestin-only contraceptives, including the etonogestrel implant, 6 weeks postpartum to be safe for both the breastfeeding mother and the breastfed infant [12, 32].

When initiated 4–8 weeks postpartum, the use of the etonogestrel implant was not associated with change in volume or composition of breast milk [33]. Additionally, no differences were noted in the infant or in the 3-year follow-up, assessing child growth and development, between implant users and copper-IUD users [33, 34].

Short-Acting Postpartum Contraception and Breastfeeding

As mentioned above, there is a theoretical concern that progestin-containing contraceptives negatively affect lactogenesis [12, 26, 28, 32]. Estrogen has also been thought to impair breastfeeding in the postpartum period via its inhibitory effect on prolactin [29, 35]. Due to these concerns, the US MEC has classified combined hormonal contraceptives as category 4 for breastfeeding women up to 6 weeks postpartum (unacceptable health risk with use) and category 3 for 6-week to 6-month postpartum (risk outweighs advantage of use) [12, 29]. It is also important to note that failure rates of short-acting contraceptive methods with "typical use" are lower than with "perfect use" and thus could result in unintended pregnancy [36, 37].

Despite these concerns, some women may prefer to use short-acting estrogen-containing contraception, such as the combined hormonal contraceptive pill, transdermal patch, or vaginal ring. Women may prefer these short-acting methods for their improvement in menstrual cramps, improved bleeding patterns, reversibility, ease of use, and noncontraceptive benefits (acne, breast tenderness, etc.) [29, 38, 39]. One RCT addressed the question of whether or not it is appropriate to offer these methods of contraception to breastfeeding women. This study examined the effect of combined hormonal contraceptives versus progestin-only containing pills on breastfeeding outcomes and infant weight and height. Investigators found no significant differences in formula supplementation or breastfeeding discontinuation at 8 weeks postpartum, nor did investigators find significant differences in infant weight or length [40]. A Cochrane review of RCTs investigating lactation patterns and infant growth in women using hormonal contraception, nonhormonal contraception, or placebo concluded that most trials did not report significant differences in breastfeeding duration, breast milk composition, or infant growth in either arm [29]. There were few exceptions to this generalization, but these findings were mostly found in older studies with limited reporting of data [29, 41].

To answer whether or not estrogen-containing contraceptives are suitable for the breastfeeding mother is not straightforward.

> While limited data has shown no differences in breastfeeding outcomes or infant growth, there is a possibility that estrogen-containing methods may inhibit prolactin secretion and therefore possibly decrease milk production [12, 29, 35, 40].

Postpartum Contraception for the Non-breastfeeding Mother

If a woman is not lactating, there is no concern of hormonal effects on lactogenesis. However, there is still a need to consider high-risk health conditions in the individual. Exogenous estradiol exposure can be contraindicated in certain health conditions, particularly those related to cardiovascular disease. The Society for Maternal-Fetal Medicine recommends that LARCs be offered to women at highest risk for adverse health events as a result of a future pregnancy (Grade 1B) [4]. Due to LARCs lacking estrogen, they have been considered safe options for women with a history of various medical conditions, including chronic hypertension, cardiovascular disease, diabetes, thromboembolic disease, cardiovascular, and epilepsy (Table 16.1) [4, 12].

Table 16.1 Conditions associated with increased risk of pregnancy-related morbidities

Obstetric complications	Maternal medical conditions
Preterm birth	Morbid obesity
Preeclampsia	Cardiovascular disease
Critical intensive care unit admission	Cancer
Peripartum cardiomyopathy	Diabetes
	Bariatric surgery within the past 2 years
	Human immunodeficiency virus
	Sickle cell disease
	Solid organ transplant within the past 2 years
	Thrombophilia
	Venous thromboembolism
	Maternal genetic disorders (including cystic fibrosis, Marfan syndrome)
	Chronic renal disease
	Chronic liver disease
	Chronic hypertension
	Drug addiction

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The US MEC categorizes LARCs as either category 1 or 2, as described above. The only cases where IUDs are category 4 (unacceptable risk) are typically those where there is acute infection or inflammation, such as in pelvic inflammatory disease or puerperal sepsis, malignancy (specifically levonorgestrel-containing IUD is contraindicated with current breast cancer), cavity distortion (as a result of fibroids or Müllerian anomaly), or Wilson's disease (specifically copper-containing IUD). The implant is considered US MEC category 4 only in the case of current breast cancer [4, 12]. For a more detailed description, please see US MEC's recommendations specific to the immediate postpartum period on the Center for Disease Control website (https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html), as well as in an app for smartphones and tablets ("Contraception").

Summary

Seventy percent of the pregnancies occurring within 1 year from delivery are unintended [3, 4]. The American College of Obstetricians and Gynecologists (ACOG) recommends that long-acting reversible contraceptive (LARC) methods, both hormonal and nonhormonal, be offered to all appropriate candidates, given their superior efficacy in preventing unintended and close-interval pregnancy compared to short-acting methods [17]. Immediate initiation of LARC reduces the risk of unintended and close-interval pregnancy [4]. If the patient desires short-acting contraception, the provider must counsel the patient on failure rates associated with "perfect use" versus "typical use" [36, 37]. Additionally, if the patient desires short-acting estrogen-containing contraception, she must be counseled on the potential for decreased milk production and any potential contraindications to receiving estrogen. Ultimately, every woman must be counseled thoroughly on the advantages and disadvantages of every contraceptive method. It is the job of the provider to use evidence-based guidelines to recommend a suitable option for the patient.

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Chapter 17
Contraception in Perimenopausal Patients

Jennifer Reeves and Carrie Cwiak

Introduction

Perimenopause is the time period 5–10 years prior to menopause (i.e., amenorrhea for 12 consecutive months) and is characterized by changes in menstrual regularity or flow, vasomotor symptoms, mood changes, sexual dysfunction, or other symptoms [1]. Physiological changes associated with the menopausal transition are due to fluctuations in pituitary and ovarian hormones, including estradiol and follicle-stimulating hormone (FSH) [2]. The median age of menopause in the United States (US) is 51 years of age. For the purposes of this chapter, we will refer to the population of reproductive persons over the age of 40 until age 55 or until menopause is assured as perimenopausal.

Despite age-related declines in fecundity (chance of a live birth per menstrual cycle), pregnancy does occur among sexually active perimenopausal patients. According to the US Census Bureau's 2012 Census Population Survey (CPS), the pregnancy rate among women older than 40 was 26 births per 1000 women, compared to 206 births per 1000 women among 30- to 40-year-olds [3]. Based on a 2014 Guttmacher review of the same 2012 CPS data, the average person of reproductive potential in the United States will have two children, and therefore women may spend over 30 years of their reproductive lives avoiding pregnancy [4]. Additionally, nearly one third of all pregnancies among women older than 40 are unintended, highlighting the contraceptive needs of this population [5].

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The increased incidence of perinatal complications among patients of advanced maternal age includes early pregnancy loss, chromosomal abnormalities, gestational diabetes, hypertensive disorders or pregnancy, preterm delivery, and intrauterine growth restriction [6]. Therefore, any sexually active person at risk of pregnancy who does not desire pregnancy should be offered contraceptive options that fit their contraceptive needs, regardless of age.

Patient Screening and Counseling on Contraception During Perimenopause

The North American Menopause Society (NAMS) recommends considering a patient's concerns and values when providing anticipatory guidance regarding the menopausal transition, including fertility, menstrual changes, and other symptomatology. Such discussions not only facilitate informed decision-making but also may improve a patient's sense of well-being [7]. Family planning, including exploring the individual's contraceptive needs, should also be incorporated into these conversations. For patients of all ages, effective contraceptive counseling incorporates shared decision-making in order to provide full information about all options as well as guide patients to methods that are safe to use in their circumstance and best fit their preferences and values. Shared decision-making must also respect the family planning needs and desires of patients who do not wish to use contraception or who choose less effective methods [8]. In counseling perimenopausal patients on contraceptive options, health-care providers should consider the risks of unintended pregnancy as well as the risks of continuing contraception until menopause on an individual basis [9].

A mixed-methods systematic review of 21 qualitative and quantitative studies evaluating the family planning needs of women over 40 revealed that educational level, awareness of available contraception, fear of side effects, religious and cultural beliefs, social standing in their community, perceived personal control, and confidentiality all impacted contraceptive choice and use among this population [10].

Evidence-Based Guidance for Specific Contraceptive Methods

The US Medical Eligibility Criteria for Contraceptive Use (MEC) and the US Selected Practice Recommendations (SPR) are two documents published by the Centers for Disease Control and Prevention (CDC), which provide evidence-based guidelines and recommendations on contraceptive use and safety [9, 11]. The MEC details contraceptive risk and safety data for a variety of medical conditions and personal characteristics, and the SPR provides practical guidelines for contraceptive initiation and use. These documents were initially modeled on the World Health

Organization (WHO) guidelines and are updated via rigorous systematic review and expert consultation approximately every 5 years [11].

By itself, age is not a contraindication to the use of any contraceptive method as there is no evidence to suggest that age alone increases the risk of contraceptive-related complications [11]. Table 17.1 is a summary of the US MEC recommendations for contraceptive use based on age (see Table 17.1). Notably, rates of contraceptive failure resulting in pregnancy are not statistically different in American women aged 30–44 compared to other age groups [12], and rates of contraceptive failure in American women aged 45 and older are not available. However, age is a risk factor for chronic medical conditions such as cardiovascular disease, diabetes, obesity, hypertension, migraine headaches, or cancer that may limit the safety of certain hormonal contraceptives. Therefore, health-care providers should consider the patient's individual medical conditions and risk factors when giving contraceptive advice rather than provide recommendations based on age alone. In this chapter, we will highlight the associated benefits and risks, including noncontraceptive benefits, of specific contraceptive methods in the perimenopausal period.

Intrauterine Contraception

Intrauterine contraceptive devices (IUCDs) provide long-acting, reversible contraception (LARC). IUCDs are available in both hormonal and nonhormonal formulations. Since little to no action is required by the user after placement, the typical failure (i.e., pregnancy) rate of both hormonal and nonhormonal IUCDs is less than 1% [12]. IUCDs provide contraception for 3–12 years depending on the formulation, which makes them ideal methods for patients who have completed or do not desire childbearing. Both hormonal and nonhormonal IUCDs are US MEC Category 1 (no limit to use) for patients over 40 years of age [11]. IUCD placement is contraindicated in patients with known or suspected pregnancy, severe pelvic infection,

Table 17.1 US Medical Eligibility Criteria for Contraceptive Use based on age

Method	Age range (years)	USMEC category
Estrogen-containing contraception	≥40	2
Progestin-only pill	≥40	1
Progestin implant	≥40	1
DMPA	≥40–45 >45	1 2
Cu-IUD	≥40	1
LNG-IUS	≥40	1

Adapted from US Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016 [11]
DMPA depot medroxyprogesterone acetate, Cu-IUD copper intrauterine device, *LNG-IUS* levonorgestrel intrauterine system
1 = a condition for which there is no restriction for the use of the method; 2 = a condition for which the advantages if using the method generally outweigh the disadvantages of using the method; 3 = a condition for which the theoretical or proven risks usually outweigh the advantages of using the method; 4 = a condition that represents an unacceptable health risk if the method is used

undiagnosed abnormal uterine bleeding, or uterine malformations [9]. Risks of IUCD placement and use are rare. There appears to be no excess or additional risk of IUCD complications (e.g., perforation, infection, expulsion) for patients older than 40 years of age [13]. All IUCDs may be inserted immediately postpartum or postabortion, except in the setting of uterine infection, without limit to patient age [9, 11]. Given their high contraceptive effectiveness, safety profile, user satisfaction rate, and continuation rate, IUCDs are considered first-line contraceptive options by many professional organizations, such as the CDC, WHO, and the American College of Obstetricians and Gynecologists (ACOG), among others [9, 14, 15].

Modern hormonal IUCDs contain levonorgestrel and are collectively referred to as levonorgestrel-releasing intrauterine systems (LNG-IUS). Levonorgestrel thickens cervical mucus, which prevents sperm entry into the upper reproductive tract and thereby prevents fertilization [16]. LNG-IUS inconsistently suppresses ovulation [17].

Although irregular vaginal bleeding and cramping may occur within the first few months of LNG-IUS placement, amenorrhea rates are as high as 18% at 1 year of use [18], due to progesterone's antiproliferative effects on the endometrium [17]. Therefore, the LNG-IUS may be an ideal contraceptive for perimenopausal patients seeking LARC.

LNG-IUS may be safely used in people with various medical conditions, including those with contraindications or intolerances to estrogen use. The LNG-IUS is US MEC Category 4 (contraindicated) for people with current breast cancer and US MEC Category 3 (risks generally outweigh benefits of use) for people with a personal history of breast cancer in the last 5 years [11]. Owing to the local distribution of progestin to the uterus, serum levels of levonorgestrel are lower with LNG-IUS use than with use of other progestin-containing contraceptives [19]. As such, there are no known interactions with other medications [9] or systemic side effects associated with use.

Modern nonhormonal IUCDs contain copper. The copper IUCD prevents fertilization by affecting both sperm motility and viability as a result of copper ion release into the uterine cavity [20]. The ParaGard T380A is the only commercially available copper IUCD in the United States. ParaGard is FDA approved for 10 years, although data suggest contraceptive efficacy up to 12 years [21]. Based on a 2014 literature review on extended IUCD use, people who are older than 35 at the time of ParaGard placement may continue use until menopause with negligible risk of pregnancy [21]. Therefore, the copper IUCD is an excellent contraceptive option for perimenopausal patients who desire a nonhormonal LARC method. Except for Wilson's disease, there are no medical conditions that are absolute contraindications to copper IUCD use and no known interactions with other medications [9]; therefore, it may be an ideal contraceptive option for perimenopausal patients with medical conditions that limit the use of hormonal contraception. Copper IUCD use may initially be associated with increased vaginal bleeding in flow and duration and increased menstrual cramping [22], though patients tend to experience no change in flow, duration, or timing with continued use compared to their baseline menstrual

pattern. Therefore, patients with dysmenorrhea or heavy menstrual bleeding may not be ideal candidates for the copper IUCD. Finally, as it is a nonhormonal method, there are no known systemic side effects associated with its use.

Systemic Progestin-Only Methods

Formulations of systemic progestin-only contraceptive methods include oral preparations, injectables, and implants. These methods are all US MEC Category 1 (no limit to use) or 2 (benefits generally outweigh risks of use) for people older than 45 and may be excellent contraceptive options for people with contraindications or intolerances to estrogen use [11].

In normotensive people, systemic progestin-only contraceptives are not associated with an increased risk of venous thromboembolism (VTE), myocardial infarction (MI), or stroke [23, 24]. As with the LNG-IUS, all progestin-only methods are US MEC Category 4 for people with current breast cancer and US MEC Category 3 for people with a personal history of breast cancer in the last 5 years [11].

The 68 mg etonogestrel (ENG) single-rod implant is marketed as Nexplanon in the United States and is a highly effective, LARC method. The ENG implant is FDA approved to provide contraception for 3 years; however, several large epidemiological studies suggest contraceptive effectiveness up to 5 years [25, 26]. Therefore, the ENG implant is another ideal method for patients who have completed or do not desire childbearing. Since little to no action is required by the user after placement, the typical use failure rate is less than 1% [12]. The ENG implant's primary contraceptive mechanism of action is through ovulation suppression, which was demonstrated in nearly 100% of cycles of ENG implant users [27]. Risks of the ENG implant are minimal at the time of placement, including localized bruising, infection, or deep placement. Similar to the LNG-IUS, irregular or prolonged vaginal bleeding may occur with ENG implant use, and this bleeding pattern may improve over time [28]. Patient satisfaction and contraceptive continuation rates are high; however, among those who discontinue use, irregular and breakthrough vaginal bleeding are the most common reasons for discontinuation [29, 30].

Finally, as with IUCDs, the ENG implant is considered a first-line contraceptive option by professional organizations, such as CDC, WHO, and ACOG [9, 14, 15].

Depot medroxyprogesterone acetate (DMPA) is the progestin-only injectable contraceptive available in the United States. It is administered intramuscularly or subcutaneously every 3 months to provide short-term, reversible contraception. The typical use failure rate of DMPA is 4% [31]. DMPA suppresses ovulation as its primary mechanism of action for contraception [31]. As a progestin-only method, irregular or unpredictable vaginal bleeding may occur within the first few injections, though bleeding

becomes lighter over time [32, 33]. Amenorrhea rates are as high as 50% at 1 year of use and increase further with prolonged use [33, 34]. Unique disadvantages of DMPA are weight gain and delayed return to fertility, both of which may impact perimenopausal patients disproportionately. DMPA use is associated with weight gain especially in high-risk populations [35], which may include patients in midlife. In addition, patients' return to fertility can be delayed by a median of 10 months after discontinuation of DMPA [32], which can be a disadvantage for patients who desire fertility after age 35. The impact of DMPA on bone health is discussed later in this chapter.

The progestin-only pill (POP), also known as the mini-pill, contains progestin (norethindrone or drospirenone in US formulations) in lower doses than in combined hormonal contraceptives (CHCs). Unlike the drospirenone POP, whose primary mechanism of action for contraception is ovulation suppression, the norethindrone POPs work primarily by thickening cervical mucus and preventing sperm entry into the upper reproductive tract [36]. Therefore, norethindrone POPs require same-time daily administration to achieve highest contraceptive effectiveness [9]. The overall typical use failure rate of POPs is 9% [12]. However, POPs have higher contraceptive efficacy in people over 40 compared to those younger than 40, most likely due to age-related declines in fecundity [31]: with perfect use, the contraceptive failure rate of POPs in people over 40 is 0.3 per 100 woman-years compared to 3.1 per 100 women-years for POP users less than 40 [37]. POPs are dosed continuously without placebo pills, which may result in bleeding pattern changes including irregular or breakthrough vaginal bleeding or amenorrhea [38].

There are minimal risks and side effects associated with POP use; therefore, this method may be preferred among perimenopausal patients who desire a short-term, estrogen-free contraceptive.

Combined Hormonal Contraception

CHCs are contraceptive formulations that include synthetic forms of both estrogen and progesterone. Currently, these include combined oral contraception (COC), commonly known as "the pill," the contraceptive patch, and the contraceptive vaginal ring. The estrogen component for formulations of CHC in the United States is either ethinyl estradiol (EE) or estradiol valerate. Progestins used in CHC vary between formulations in their potency and side effect profile. CHC requires user adherence on a daily (pill), weekly (patch), or monthly (ring) basis. The typical use failure rate of CHC is 9% [12]. CHC prevents pregnancy through the mechanistic actions of progesterone, namely, ovulation suppression and thickening cervical mucus. The estrogen component of CHC provides stabilization of the uterine lining, which balances the endometrial thinning that also occurs with progestin. CHC also provides the option for a cyclic bleeding pattern.

For healthy patients older than 40, CHCs are US MEC Category 2. This recommendation comes from inconsistent evidence on CHC's effect on bone health (discussed later in this chapter) and cardiovascular disease [11].

Briefly, baseline cardiovascular risk increases with age, and the use of estrogen-containing contraceptives has been associated with increased incidence of cardiovascular events in people with other cardiovascular risk factors [39].

Therefore, US MEC recommendations for CHC are generally Category 3 or Category 4 for people with cardiovascular risk factors (see Table 17.2). For example, in reproductive people over the age of 35, light and heavy tobacco use is a relative or an absolute contraindication, respectively, for CHC use [11].

Perimenopausal users may be concerned about the risks of arterial or venous thrombosis in considering CHC use. Older age is an important risk factor for MI and ischemic stroke; however, CHC has also been associated with increased risk of arterial thrombosis. A 2015 Cochrane Review and meta-analysis of 24 observational studies showed a moderately increased risk of MI (relative risk (RR) 1.6, 95% confidence interval (CI) 1.2–2.1) and ischemic stroke (RR 1.7, 95% CI 1.5–1.9) among current CHC users compared to nonusers [39]. Incidence of VTE also increases with older age, and CHC use has also been associated with higher VTE incidence [40]. In CHC users under 50 years of age, odds of VTE were five times higher than that of nonusers (odds ratio (OR) 5.0, 95% CI 4.2–5.8), with the highest

Table 17.2 US Medical Eligibility Criteria for Contraceptive Use for CHC

Medical condition or characteristic	US MEC category
Smoking, age ≥ 35	
<15 cigarettes/d	2
≥15 cigarettes/d	4
Obesity (BMI ≥ 30)	2
Hypertension	
Controlled hypertension	3
Elevated BP: systolic 145–159 mmHg or diastolic 90–94 mmHg	3
Elevated BP: systolic ≥160 mmHg or diastolic ≥95 mmHg	4
Vascular disease	4
Diabetes	
No vascular disease	2
Vascular disease or ≥ 20 years' duration	3, 4 (based on severity of condition)
Stroke	4
Current or history of ischemic heart disease	4
Multiple risk factors for cardiovascular disease (e.g., older age, smoking, obesity, diabetes, hypertension)	3, 4 (based on severity of condition)

Adapted from US Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016 [11]
CHC combined hormonal contraception, *BMI* body mass index, *BP* blood pressure
1 = a condition for which there is no restriction for the use of the method; 2 = a condition for which the advantages if using the method generally outweigh the disadvantages of using the method; 3 = a condition for which the theoretical or proven risks usually outweigh the advantages of using the method; 4 = a condition that represents an unacceptable health risk if the method is used

odds occurring within the first 3 months of use (OR 12.6, 95% CI 7.1–22.4), but VTE odds declined with duration of CHC use [41]. Importantly, absolute risk of VTE remains low, even with CHC use, and VTE events are more common during pregnancy or postpartum than during CHC use in all age groups [42].

In summary, healthy people without cardiovascular risk factors can safely use CHC until menopause. CHCs are a contraceptive option for those perimenopausal patients who desire a short-term method that allows the option of a lighter but regular bleeding pattern. Cyclic use of CHC includes a hormone-free interval every 21–24 days, thus mimicking a regular menstrual pattern. For those people who desire less bleeding or fewer menstrual-related symptoms, CHC use may be extended (hormone-free interval fewer than 4–7 days) or continuous (no placebo week).

Permanent Contraception

Permanent contraception for biologic females is achieved by surgically occluding, ligating, or removing the fallopian tubes. The timing of transabdominal tubal ligation or removal can be immediately postpartum or postabortion in patients without pregnancy-related complications or as an outpatient procedure unrelated to pregnancy. Permanent contraception for biologic males is achieved via vasectomy, in which the vas deferens is ligated bilaterally. Vasectomy is performed as an outpatient procedure with minimal or local sedation. Since little to no action is required by the user after permanent contraceptive surgery, the typical failure (i.e., pregnancy) rate is less than 1% [12]. Permanent contraception is an option for perimenopausal patients who have completed or do not desire childbearing, especially if they have medical conditions that limit the use of other contraceptives. There are no medical conditions that are contraindications to permanent contraceptive use, although patients need to be good surgical candidates [9].

Preoperative counseling for tubal ligation/removal should emphasize the permanency of the procedure. The risk of regret is decreased in women over 30 years of age compared to their younger counterparts [43]. Because it is a nonhormonal method, there is no impact on ovulation or menstruation, and so patients will experience no change in flow, duration, timing, or related symptoms from their baseline menstrual pattern. Therefore, patients with heavy menstrual bleeding or dysmenorrhea may not be ideal candidates for permanent contraception. Patients with preexisting menstrual-related disorders previously treated by hormonal contraception will note a return of their symptoms once tubal ligation is complete and hormonal contraception is ceased. This may be perceived to be caused by the tubal ligation, when in fact it is a sign that hormonal treatment may need to be restarted or other treatment be considered. Similarly, there are no systemic side effects associated with the use of permanent contraception.

Coitally Dependent Contraception

Coitally dependent contraceptive methods include male condom, female condom, diaphragm, vaginal contraceptive sponge, spermicide, cervical cap, fertility awareness-based methods, and coitus interruptus. Overall, typical use failure rates of these methods are higher compared to all other contraceptive methods discussed in this chapter. Since perimenopausal patients have decreased fecundity, unintended pregnancy rates may be lower with their use. However, it is unclear how effective fertility awareness-based methods are for perimenopausal patients. Fertility awareness-based methods utilize menstrual cycle timing or signs of ovulation (e.g., basal body temperature, cervical mucus thickening) to identify the fertile time during each menstrual cycle when sexual intercourse should be avoided if pregnancy is not desired.

Overall, the typical use failure rate for fertility awareness-based methods is 15% [31]. For perimenopausal patients who are no longer ovulating or menstruating regularly, fertility awareness-based methods may be less reliable.

Barrier-based contraception also reduces the risk of sexually transmitted infections (STIs), which is important to consider in this population. Regardless of age, all patients should be counseled on dual protection, which is the use of one or more concurrent methods to prevent both unintended pregnancy and STIs. All people, including those with diverse sexual relationships or practices, can benefit from education on the various forms of dual protection, regardless of primary contraceptive method used [44].

Emergency Contraception

The same emergency contraceptive options available to younger reproductively aged patients are also available for patients in perimenopause. These include oral levonorgestrel, oral ulipristal acetate, and the copper IUCD.

Both oral options prevent fertilization by delaying ovulation, whereas the copper IUCD is spermicidal. Among all options, the copper IUCD is the most efficacious at preventing pregnancy (less than 1 in 1000 failure rate when placed within 5 days of unprotected sex) [45]. An added benefit of using the copper IUCD as emergency contraception is that it may be continued as ongoing contraception [46]. Oral levonorgestrel is FDA approved for use within 72 hours of unprotected intercourse, whereas ulipristal acetate is FDA approved for use within 5 days. In a randomized

non-inferiority study, ulipristal acetate was as effective as levonorgestrel if used within 72 hours of unprotected intercourse (OR 0.68, 95% CI 0.35–1.31) [47].

Importantly, oral emergency contraception has not been specifically studied in perimenopausal populations [48]. However, perimenopausal patients who use coitally dependent methods or who have sex on an infrequent basis may desire to have oral emergency contraception on hand in case of method failure, misuse, or nonuse. There are no specific exceptions or special instructions for emergency contraceptive use based on age alone, and all methods of emergency contraception are US MEC Category 1 or 2 with comorbid medical conditions [9, 11]. All sexually active patients at risk for unintended pregnancy, regardless of age, should be counseled on emergency contraception in addition to other contraceptive options.

Noncontraceptive Health Benefits of Hormonal Contraception

In addition to providing birth control, the noncontraceptive health benefits of hormonal contraception are numerous and well studied. Among patients in the perimenopausal transition, hormonal contraception may control abnormal uterine bleeding (AUB), alleviate vasomotor symptoms, or modify the risks of developing certain cancers (see Table 17.3).

In the following paragraphs, we detail the evidence that supports various noncontraceptive health benefits of hormonal contraception, especially where relevant to patients in perimenopause.

Table 17.3 Noncontraceptive benefits of hormonal contraception for perimenopausal patients

Restoration of regular bleeding (CHC)
Reduced heavy menstrual bleeding
Reduced anemia
Reduced dysmenorrhea
Relief from vasomotor symptoms (CHC)
Prevention of endometrial hyperplasia and cancer
Prevention of ovarian cancer
Possible prevention of osteoporotic fractures (CHC)
Improvements in acne that may flare up with perimenopause (CHC)

Adapted from Miller et al. 2018 [77]
CHC combined hormonal contraception

Abnormal Uterine Bleeding (AUB)

Menstrual cycle irregularities, including changes in cycle frequency and heavy menstrual bleeding, are common during perimenopause [7]. Although there may be many causes of AUB in reproductive individuals over the age of 40, oligomenorrhea is most commonly caused by anovulatory cycles as a result of the physiologic decline in ovarian function. Importantly, health-care providers should consider a wide differential diagnosis with the presentation of AUB in this age group, including endometrial hyperplasia or carcinoma, leiomyomata, and thyroid disease [49]. Further, pregnancy should be excluded in any sexually active person who presents with AUB.

Several formulations of hormonal contraception have demonstrated effectiveness in reduction of and regulation of menses. The LNG-IUS is FDA approved for the treatment of heavy menstrual bleeding (HMB). LNG-IUS use is associated with decreased menstrual blood loss, improvement of anemia, improvement in dysmenorrhea, and improvement in symptomatic fibroids or adenomyosis [50]. In a 2015 Cochrane Review, women diagnosed with HMB who were randomized to LNG-IUS reported decreased menstrual blood loss, higher quality of life scores, and higher continuation rates at 2 years compared to those randomized to oral therapy (e.g., progesterone, COCs, mefenamic acid) [51]. LNG-IUS use is associated with amenorrhea in 45% and 50% of patients at 6 and 12 months, respectively [52]. In a prospective cohort study of LNG-IUS users aged 18–45, amenorrhea was significantly associated with LNG-IUS satisfaction and continuation, highlighting the importance of this noncontraceptive benefit to LNG-IUS users [53].

LNG-IUS use has been shown to increase serum hemoglobin values by up to 1.6gm/dl over 5 years in one study [54]. Among patients with adenomyosis, LNG-IUS use has been associated with decreased number of bleeding days, decreased dysmenorrhea, and increased serum hemoglobin values compared to pre-insertion [55]. Among patients with uterine fibroids, LNG-IUS use leads to substantial reductions in menstrual blood loss and significant decreases in uterine volume as measured by transvaginal ultrasound [56], though clinical results may vary depending on the number, size, and location of the fibroids [57]. Improvement in HMB with LNG-IUS use in perimenopausal patients is similar to that of endometrial ablation [58]. And LNG-IUS is more cost-effective than hysterectomy and may be specifically preferred for the management of AUB or HMB in people with multiple medical comorbidities or who are otherwise poor surgical candidates [50, 51].

Other progestin-only methods of hormonal contraception may also be considered by perimenopausal patients who desire decreased menstrual bleeding as a noncontraceptive benefit and can tolerate irregular bleeding patterns. For example, up to 60% of DMPA users may be amenorrhoeic after 12 months; however, irregular vaginal bleeding was a frequent reason for discontinuation [59]. POPs and the ENG implant are also associated with decreased menstrual blood loss, though both may be associated with increased frequency of unscheduled bleeding, which may also result in discontinuation among perimenopausal patients with AUB [30, 38].

CHCs are commonly used to treat HMB and may be used in perimenopausal patients without contraindications or intolerances to estrogen. In a 2019 Cochrane Review, COCs had five times greater odds of decreased menstrual blood loss compared to placebo (OR 5.15, 95% CI 4.40–111.12) [60]. From the same systematic review, limited evidence suggested that the contraceptive vaginal ring had similar effects in decreasing menstrual blood loss as COCs [60]. A 2014 Cochrane Review comparing continuous or extended-cycle CHC use to cyclic CHC use found decreased number of bleeding days among continuous CHC users; however, some studies had increased discontinuous rates among continuous users due to unscheduled vaginal bleeding [61]. The same review concluded that continuous or extended-cycle CHC use may be associated with decreased menstrual symptoms (e.g., headache, menstrual pain), which may be an additional benefit to menstrual regulation among perimenopausal patients [61]. CHC formulations with higher than 20 mcg EE are associated with less unscheduled or irregular bleeding, which may be desirable to perimenopausal patients with AUB [62]. The decision of which formulation, and whether to use CHC continuously or cyclically, should be based on patient goals and shared decision-making.

Vasomotor Symptoms

CHC often reduces vasomotor symptoms in perimenopausal patients, more so for those with severe symptoms or who use CHC continuously (i.e., eliminating the hormone-free interval) [63]. In a prospective cohort of perimenopausal women, COC use was associated with a 40% incidence of hot flushes compared to a 90% incidence with nonuse [64]. In women over 40, the use of a 20 mcg COC and daily supplementation with 10 mcg of EE during the hormone-free interval statistically significantly reduced vasomotor and mood symptoms compared to standard COC regimen [65]. The proposed mechanism of action involves stabilization of fluctuating and low circulating estradiol levels [66]. DMPA has also been shown to relieve vasomotor symptoms in perimenopausal patients [67, 68].

Endometrial Hyperplasia and Cancer

Older age and exposure to unopposed estrogen (e.g., anovulatory cycles, exogenous hormone use) are important risk factors for the development of endometrial hyperplasia and cancer [69, 70]. Progesterone counteracts the effects of estrogen in the endometrium, and systemic progestins have been used to prevent and treat proliferative endometrium, including hyperplasia and malignancy [71].

IUCDs and hormonal contraceptive methods have also been shown to decrease endometrial cancer risk and may be an important consideration for perimenopausal patients choosing a contraceptive method.

In a 2015 pooled analysis of 18 epidemiological studies of hormonal and nonhormonal IUCD use and endometrial cancer risk, any IUCD use was associated with decreased risk of endometrial cancer compared to never users (pooled OR 0.81, 95% confidence interval (CI) 0.74–0.90) [72]. In the same study, groups of age ≥ 35 at first IUCD use and ages 40–44 and ≥ 45 at last IUCD use showed greater decreases in endometrial cancer risk than younger age groups: pooled ORs 0.53 (95% CI 0.43–0.67), 0.58 (95% CI 0.44–0.75), and 0.60 (95% CI 0.50–0.72), respectively [72]. The authors discussed that their findings point to the likely complex mechanism of IUCD effect on the uterine endometrium and the resulting decreased development of endometrial hyperplasia or malignancy. Specifically with LNG-IUS that releases progestin directly to the uterus, a large Norwegian, population-based, prospective cohort found that ever users of LNG-IUS had a strongly decreased risk of endometrial risk (risk ratio (RR) 0.22, 95% CI 0.13–0.40) compared to never users [73].

More recently, LNG-IUS has been studied in the nonsurgical management of endometrial hyperplasia and low-grade endometrial carcinomas. In a recent retrospective case series, 32 patients diagnosed with complex atypical hyperplasia and early-grade endometrial cancer who were not candidates for hysterectomy were treated with LNG-IUS. At repeat biopsy in 6 months, 75% of all participants had restoration of normal endometrial histology [74]. In other comparative studies, LNG-IUS had similar resolution rates of endometrial hyperplasia compared to oral progestins, making them a cost-effective and low-risk alternative to systemic progestin therapy [75, 76].

LNG-IUS may be an ideal method in perimenopausal patients who desire highly efficacious contraception and continued endometrial protection after initiation of hormone therapy (HT). The 52 mg LNG-IUS is licensed in many countries for endometrial protection; however, this indication is off-label use in the United States [77].

The lower doses of LNG-IUS (i.e., 13.5 mg and 19.5 mg) have not been studied for this indication. In a recent clinical review, concurrent LNG-IUS use during estrogen therapy has demonstrated an absence of endometrial hyperplasia and increased amenorrhea rates, providing endometrial protection for up to 5 years [78]. Further, IUCD use for endometrial protection during HT may be preferred to oral progestins due to decreased systemic side effect profile of abdominal bloating and weight gain [50, 79]. LNG-IUS has also demonstrated prevention of endometrial polyp formation in postmenopausal patients on oral tamoxifen for adjuvant endocrine therapy of estrogen receptor-positive breast cancer; however, studies were not powered to determine endometrial cancer risk or breast cancer recurrence risks [80].

COC use is associated with decreased endometrial cancer risk. One of the first studies to assess this was a US population-based case-control study, which demonstrated that any COC use for at least 12 months was associated with a 40% reduction in endometrial cancer, a reduction which persisted up to 15 years after COC discontinuation [81].

A more recent systematic review in 2010 identified more than 15 case-control and 4 large cohort studies, which report an approximately 50% risk reduction in endometrial cancer with ever-use of COC [82]. COC use has been recommended as an endometrial cancer prevention strategy due to persistent endometrial protection up to 30 years after cessation, depending on the length of time used [83]. Although less studied, the contraceptive patch and the vaginal ring likely have similar risk reductions in endometrial cancer due to their similar formulations, mechanisms of action, and physiologic response in the endometrium as COC [31]. Among perimenopausal patients without contraindications to CHC use, CHC use for concurrent contraceptive use and endometrial cancer reduction is supported.

For patients with contraindications to estrogen use, POPs have also been associated with endometrial cancer risk reduction, although the sample size of exclusive POP users was small in the previously noted studies [82]. DMPA has also been studied in context of endometrial cancer risk. In a 1991 WHO case-control study,

> DMPA use was associated with an 80% reduced risk of endometrial cancer, which persisted up to 8 years after discontinuation [84].

Ovarian Cancer

> Older age and ovulation are important risk factors for the development most types of ovarian malignancies [85]. Multiple formulations of hormonal contraception have been associated with decreased risk of ovarian cancer, which may be an important noncontraceptive benefit for perimenopausal individuals in selecting a contraceptive method.

LNG-IUS use is associated with decreased ovarian cancer risk. In a large Finnish cohort of LNG-IUS users, ovarian cancer risk was decreased by 40% compared to cancer incidence among the general population (standardized incidence ratio 0.60, 95% CI 0.45–0.76) [86]. The theorized mechanism of action of this observation is suppression of ovulation and reduction of retrograde transportation of endometrial epithelial cells, although actual physiological data are limited [86, 87].

Multiple studies have demonstrated the protective effect of COC use against ovarian cancer. A 2013 meta-analysis of 24 observational studies found a nearly 30% reduced odds of developing ovarian cancer among COC ever users compared to never users (OR 0.73, 95% CI 0.66–0.81) [88]. More recently, a large prospective cohort study in the United Kingdom that followed over 40,000 women for more than 40 years found that ever users of COCs had a reduced lifetime risk of ovarian cancer compared to never users (incidence rate ratio 0.81, 95% CI 0.50–0.89) [89].

Data regarding DMPA use and ovarian cancer may also suggest a protective effect. The largest case-control study evaluating DMPA found a 39% risk reduction of epithelial ovarian cancer risk among DMPA ever users, which improved to 83%

if DMPA was used for 3 or more years [90]. However, earlier studies had demonstrated no statistically significant alteration in ovarian cancer risk [91].

Tubal ligation/removal is associated with decreased ovarian cancer risk. Regardless of the method, women who had transabdominal tubal ligation had a significant reduction in ovarian cancer risk (RR 0.61, 95% CI 0.46–0.85) compared to women without tubal ligation [92].

Colorectal Cancer

A prospective cohort of over 40,000 women in the United Kingdom who were followed for more than 40 years demonstrated a statistically significant risk reduction of colorectal cancer among COC ever users compared to never users (incidence rate ratio 0.81, 95% CI 0.66–0.99) [89]. A similar risk reduction was also identified in an earlier meta-analysis of eight case-control studies [93].

> The mechanism of colorectal cancer risk reduction is poorly understood and likely complex; however, decreased colorectal cancer risk may be an important noncontraceptive health benefit of hormonal contraceptive use among reproductive age patients over 40.

Breast Cancer

Breast cancer is one of the most common malignancies in the United States and may be an important concern among older reproductive age people. Several risk factors are associated with breast cancer, including older age, alcohol use, and nulliparity [85]. All forms of hormonal contraception are US MEC Category 4 for current breast cancer and US MEC Category 3 for breast cancer diagnosis in the last 5 years [11].

> However, there are no restrictions for use of hormonal contraception for benign breast conditions, family history of breast cancer, or BRCA 1/2 mutation carriers. Perimenopausal patients should consider their personal risk factors for breast cancer when choosing or continuing a form of hormonal contraception; however, they need not be recommended to discontinue or change contraception based on these data alone.

In the previously mentioned Norwegian cohort, LNG-IUS ever users had a small increased risk of breast cancer when compared to the general population but, importantly, no increase in breast cancer risk (RR 1.03, 95% CI 0.91–1.17) compared to never users [73]. These data suggest that any increased risk of breast cancer

among the population of LNG-IUS users is likely not related to the LNG-IUS itself but other factors related to choosing the LNG-IUS. The 2017 Danish Sex Hormone Register Study similarly noted that LNG-IUS users had a small but statistically significant risk of breast cancer incidence (RR 1.21, 95% CI 1.11–1.33), compared to the general population [86, 94]. No long-term data are available for LNG-IUS use and breast cancer risk.

In a landmark 1996 analysis of 54 epidemiological studies, current COC users were noted to have a small but statistically significant increase in breast cancer incidence (RR 1.24, 95% CI 1.15–1.33); however, there was no excess risk of breast cancer compared to never users 10 years after discontinuation [95]. Importantly, many of these studies included older formulations of COCs with a higher estrogen content, which may have contributed to increased risk. A more recent prospective cohort from the Danish Sex Hormone Register Study confirmed a modest increased risk of breast cancer among current COC users (RR 1.2, 95% CI 1.14–1.26). Their analysis demonstrated an apparent duration-response relationship with duration of use, with 10 or more years of COC use having the greatest risk (RR 1.38, 95% CI 1.26–1.51) [94].

However, in the 2017 UK cohort, there was no increased long-term risk of breast cancer among ever users compared to never users, from which the authors speculate that any increased risk among current or recent users observed in other studies may reverse after 5 years of discontinuation [89]. A large case-control study conducted by the CDC that included women aged 35–64 also found no statistically increased risk of breast cancer among current or ever users of COC regardless of formulation, duration of user, and family history [96].

Progestin-only formulations of contraception may also be associated with no or slightly increased risk of breast cancer. In a systematic review, only one of six studies found an association between progestin-only contraceptive use and breast cancer: a case-control study that noted an increased risk of breast cancer among DMPA users aged 35–44 years compared to never users (RR 2.3, 95% CI 1.3–4.1) [97]. The Danish Sex Hormone Register Study reported few breast cancer diagnoses among contraceptive implant and DMPA users; therefore, breast cancer risk was nonsignificant [94].

Bone Health

Bone health and prevention of fractures may be an important consideration in decisions about contraceptive use among older reproductive patients. Age-related decreases in bone mineral density (BMD) increase fracture risk, and estrogen is important to bone health, including remodeling and preservation of bone density [98, 99].

Data are mixed as to the effects of hormonal contraception on BMD and fracture risk in premenopausal patients. And yet, hormonal contraception may be safely continued throughout the menopause transition and should not be either continued or discontinued for concerns over bone health.

In a Swedish case-control study of postmenopausal women, ever-use of COC was associated with a 25% reduction in hip fracture risk (OR 0.75, 95% CI 0.59–0.96); however, data were collected retrospectively via self-report [100]. Among a prospective case-control study of 40–49-year-old women in South Africa, no significant difference in forearm BMD was observed in hormonal contraceptive users compared to nonusers at baseline or at 2.5-year follow-up [101]. Based on limited data, the vaginal ring and contraceptive patch appear to have little effect on BMD in premenopausal women [102, 103]. There are no studies that indicate a negative effect of POPs, contraceptive implants, or LNG-IUS on BMD [13, 104].

Current DMPA use has been associated with lower BMD compared to nonusers, confirmed by a recent Cochrane Review of randomized controlled trials [105]. Decreases in BMD associated with DMPA use appear to plateau at 2 years of use and mirror BMD loss observed during pregnancy and lactation [104]. Decreases in BMD among DMPA users below 35 years of age are reversible as soon as 2 years after discontinuation [106]. Specifically, studies of perimenopausal women have shown that decreases in BMD associated with DMPA use appear to plateau after 1 year of use and are similarly reversible after discontinuation [107]. While two observational studies have found modest increases in fracture risk among DMPA users, they did not adequately control for potential confounders such as smoking, body mass index, and trauma [77]. In fact, a retrospective study found that DMPA users had a baseline increased risk of fracture (RR 1.28, 95% CI 1.07–1.58) compared to nonusers [108].

Discontinuation of Contraception

The age at which a person of reproductive potential is no longer at risk for pregnancy is highly variable, although 85% of American women are menopausal by age 55 [109]. CDC and NAMS guidelines recommend that reproductive people who wish to avoid pregnancy continue contraception until menopause is assured or age 55, whichever occurs first [7, 9]. As previously stated, menopause is a retrospective diagnosis based on amenorrhea without hormone use for 12 months. Given that the perimenopausal transition may be characterized by a long period of irregular menses, it may be difficult for patients and their providers to know when menopause has occurred and when contraception can be safely discontinued. However, with hormonal contraception, amenorrhea is common and so the absence of either scheduled or unscheduled bleeding may not be an accurate diagnostic sign. Currently, there are no definitive laboratory tests available to diagnose when fecundity is no longer possible. Although elevated levels of FSH are consistent in postmenopausal people, this serum marker in perimenopausal people is variable, and therefore ACOG does not recommend FSH testing for confirmation of menopause [109]. In addition, hormonal contraception may falsely alter FSH levels, rendering them inaccurate for diagnosis.

In perimenopause, copper IUCD and coitally dependent method users can still rely on the absence of menses for 12 months as diagnostic of menopause. Arguably, these patients may choose to initiate menopausal hormone therapy (HT) for symptom relief before 12 months has elapsed, as long as their nonhormonal method of contraception is used consistently and correctly and they have no contraindications to HT. Hormonal contraceptive users may continue to use CHC and progestin-only methods until age 55, as long as they have no contraindications to contraceptive doses of estrogen or progestin, respectively [7, 9].

Health-care providers should regularly reassess patients for the development of contraindicating medical conditions and risk factors, in order to recommend safer options accordingly [11]. Alternatively, these patients may wish to switch to a nonhormonal method and track their menses until menopause is assured.

Whether by age or amenorrhea, once menopause has been diagnosed and hormonal contraception has been discontinued, patients may choose to initiate menopausal HT for symptom relief as long as they have no contraindications to HT. Patients should be counseled that menopausal HT should not be relied on to provide protection from unintended pregnancy.

Conclusion

Reproductive people older than 40 years of age continue to be at risk of unintended pregnancy until menopause. The complete range of contraceptive options is available to older reproductive patients, including those in perimenopause. In counseling perimenopausal patients on contraceptive options, health-care providers should consider the risks of unintended pregnancy as well as the risks of continuing contraception until menopause on an individual basis [9]. Hormonal contraception is cautioned or contraindicated in perimenopausal patients with certain medical conditions and characteristics like tobacco use, hypertension, migraine headaches, or personal history of breast cancer. However, many options can still be considered for use in people with many other common medical conditions [11]. There are several important noncontraceptive health benefits associated with hormonal contraception use in this age group, including controlling AUB, alleviating vasomotor symptoms, and modifying certain cancer risks.

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Chapter 18
Contraception in the Adolescent

Terez Yonan and Claudia Borzutzky

Contraception is an essential health-related service for all adolescents. Although many providers are comfortable in providing these services to adults, often contraception becomes a difficult topic to address when working with adolescents. This chapter will review the reasons why contraception is important to this population, discuss barriers to care, discuss confidentiality and consent as it pertains to contraception for adolescents, and review the safety of available contraceptive methods available in the general adolescent population and in specific sub-groups of adolescents.

Sexual Activity in Adolescents

According to the CDC's 2017 Youth Risk Behavior Survey (YRBS), about 40% of high school students have ever been sexually active, with 29% reporting they are currently sexually active and nearly 10% reporting four or more lifetime partners [1]. Data trends from YRBS over the last 10 years indicate that report of condom use at last intercourse has been dropping, down from 62.8% in 2005 to 53.8% in 2017. Although the reports of nonbarrier contraception use are low, it is gradually increasing and was nearly 30% in 2017. However, only 8.8% of adolescents report dual use, that is, simultaneous use of hormonal or intrauterine contraceptives with condoms [1].

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There are several potential unintended outcomes for sexually active adolescents, including unintended pregnancy and sexually transmitted infections (STI), both major sources of morbidity in adolescents [1]. Safe sexual practices that employ condoms and contraception can prevent such unintended consequences. In 2017, there were nearly 200,000 infants born to females age 15–19 [2]. Although the U.S. teen birth rate has been declining since 2009, it remains higher than in other developed countries [2]. Furthermore, teen births disproportionately affect populations of color and can exacerbate economic and health disparities for adolescent parents. The teen birth rate is the highest in Hispanic and Black adolescents [2]. Improving access to contraception has been the key to decreasing teen birth rates across the United States and remains an important intervention that can improve health outcomes.

Although improving access to care for adolescents typically centers around issues related to transportation or cost related to medical services, consent and confidentiality are additional important aspects of access to care that those providing contraceptive care to teens should be familiar with.

Consent

The ability to consent to care is a common concern among adolescent patients and their providers. While patients under age 18 years need parental consent for most medical care, minors are able to consent on their own to some aspects of care as outlined by several legal exceptions. Although laws vary by state, the most common exceptions allow minors to legally give permission for sensitive health care services [3], including sexual and reproductive health care, mental health services, and alcohol and substance use disorder treatment. Sexual and reproductive health care includes contraception, pregnancy-related care, prevention, diagnosis, and treatment of STI, and examination and treatment after sexual assault. The age of minor consent varies by state and individual treatment type, but in many states, minors 12 and older may consent to sexual health services, and in some there is no minimum age [3, 4]. Providers should be familiar with the local laws that govern their ability to provide sensitive services to minors. Providers should also be aware that laws pertaining to abortion services are not the same laws pertaining to other sensitive services. Providers practicing in states without minor consent laws for certain services are often able to obtain patient consent nonetheless, under the mature minor doctrine [5, 6]. The Guttmacher Institute website is a useful resource that contains up to date information regarding minor consent laws across the United States [3, 7]. Although individual state laws typically govern a minor's ability to consent to care, there are a few aspects of minor consent governed by federal law [8]. This most often applies to minors who are seeking care for pregnancy. Legally emancipated minors can consent to any aspect of their care; providers should be aware that the legal definition of an emancipated minor varies by state [7].

The concept of informed consent is of the utmost importance with patients of all ages. When obtaining informed consent, providers must take into account the recommended procedure or treatment, the minor's ability to understand the benefits and complications of the procedure or treatment as explained by the provider, and the minor's ability to understand the implications and/or outcomes of the procedure or treatment. Obtaining informed consent not only relates to obtaining permission, but also includes outlining confidentiality for minor patients [7, 9].

Confidentiality

Confidentiality is a common concern expressed by a majority of minors when seeking care. Confidentiality pertains to the control of information held in the patient's medical record and whether information from the medical record can be shared with other providers, parents/guardians, or schools, etc. For the most part, minors who seek sensitive services are ensured of confidentiality; their medical information cannot legally be shared with any other entity unless the minor signs a release of information specific to that service. Although adults expect confidentiality when accessing the health care system, adolescents are not always aware of their rights to confidentiality. Thus, they often hesitate to share sensitive information with their providers, especially at their initial visit. Providers can decrease adolescent patients' hesitation by clearly outlining confidentiality and its limits. Having this discussion early in the patient–provider relationship helps build rapport and gain the adolescent's trust, whether or not they are a minor.

As mandated reporters, providers must break a patient's confidentiality if the adolescent (1) is thought to be at risk of harming him/herself (2) may harm another person or (3) discloses sexual or physical abuse or neglect (or if the provider suspects abuse or neglect), which must be reported to the local child protective services. In such instances, it is recommended that providers discuss reasons for breaking confidentiality with the adolescent patient prior to providing such information to parent(s) or the authorities. The scope and detail related to reporting laws vary by state, in particular when reporting minor sexual activity [9–11].

Access to Care for Adolescents

Adolescents face many barriers when attempting to access health care services. Barriers that commonly affect this population include lack of financial resources, lack of transportation, inability to navigate or afford public transportation, inability to access confidential health care services during school hours, inability to schedule appointments by phone, and recurrence of these barriers when trying to return for subsequent appointments [12]. These commonly reported barriers affect teens in variable ways, depending on their ethnicity, socioeconomic status, and location.

Providers who are aware of these barriers can help to improve adolescent access to care. Clinics may offer extended hours or offer public transportation tokens/vouchers [12]. Adolescents often seek services through clinics or programs that offer multiple services without the need to see other providers or travel to different locations. As discussed, ability to consent, and assurances of confidentiality and privacy are critical for adolescent patients. Adolescent patients will abstain from care when they do not feel that they will receive these basic rights related to health care [13].

> Providers can encourage adolescents to engage in care simply by posting information, such as information on the privacy policy or informed consent, in patient rooms as well as in the waiting room [14].

In order to encourage adolescents to discuss their sexual health, providers should also adopt a culturally competent, sex-positive approach [14]. A sex-positive approach begins with asking questions that help guide medical counseling, rather than making assumptions; ask about a patient's sexual attraction, orientation, and practices. Dispensing free condoms is a sex-positive, adolescent-friendly service that medical clinics can also offer [14]. It is recommended that providers involve adolescents in making medical decisions, rather than dictating their care. This engages the patient, builds rapport, and improves likelihood of initiation and continuation of the treatment plan [13, 14]. It is also recommended that providers encourage the adolescent patient to engage their parent(s) in such discussions and decision-making. This can help improve the bond between the adolescent and their parent(s), in addition to their communication.

> Of note, adolescents whose parents are engaged in their care in a positive manner are more likely to delay sexual debut, less likely to abuse substances, more likely to engage in their own care, have lower rates of psychiatric illness, and have better school performance [12].

Contraceptive Counseling for Adolescents

The CDC recommends that providers review a Reproductive Life Plan (RLP) with all patients with reproductive potential, no matter their gender [15]. The Family Planning National Training Center (FPNTC) outlines how a provider can review an RLP with a patient, using the patient-centered PATH framework: *P*arenthood/*P*regnancy Attitude, *T*iming, and *H*ow important is pregnancy prevention? The FPNTC outlines several questions providers can utilize during the patient interview to assess a RLP [16]:

- "Do you think you might like to have (more) children at some point?"
- "When do you think that might be?"
- "How important is it to you to prevent pregnancy (until then)?"

While the above questions will prompt the patient to consider contraception, providers can further understand the patient's contraceptive needs by asking, "Do you have a sense of what is important to you about your birth control?" [16]. The Adolescent Health Working Group recommends initiating the discussion of contraception by inquiring about what methods the adolescent patient is aware of and what method they are interested in [17].

When providing contraceptive counseling, the CDC and ACOG recommend that providers present the patient with a "menu of options" of contraceptive methods [18]. These organizations also recommend discussing contraceptive options from most to least effective at preventing pregnancy, including a discussion of their associated benefits and side effects.

While some patients prefer to rely on abstinence for pregnancy prevention, the abstinence-only approach is not supported by public health and medical science literature regarding teen pregnancy prevention. Abstinence is not a real-world solution for prevention of pregnancy or STI, as today's youth are waiting longer until marriage and need more realistic resources to protect their sexual health and livelihood [19]. Providers can refer to Part 1 of this text for more information on each available contraceptive option.

The National Campaign to Prevent Teen and Unintended Pregnancy (The Campaign) has several recommendations that providers can employ to help improve utilization of the most effective birth control methods, the long-acting reversible contraceptives (LARC), which include intrauterine devices (IUD) and the subdermal contraceptive implant [20].

The Campaign recommends that in addition to reviewing a young woman's reproductive life plan, providers should begin with a discussion of the patient's needs, concerns, and expectations about contraceptive methods they are interested in. This approach will help patient choose contraception that best suits their lifestyle. Focus group data indicate that providers should focus on the LARC methods first in contraceptive counseling, emphasize that these methods are "'low maintenance' and require no further action by the patient after placement." It is recommended that providers discuss other patients' experiences with the method(s) reviewed and provide information on how it will feel for the patient him/herself, as well as for their partner(s). Counseling should include discussion of the reversibility of each method as well as return of fertility after discontinuation [20]. Providers are

encouraged to refer to The Campaign's website for further contraceptive counseling recommendations and resources (https://powertodecide.org/).

In addition to discussing the available contraceptive options, ACOG recommends informing adolescent patients about emergency contraception (EC) [21, 22].

EC is effective for preventing pregnancy for up to 120 hours after unprotected/under-protected intercourse or condom failure. Although the levonorgestrel EC tablet is available over the counter, adolescent patients have improved access to this EC method when clinicians provide an advanced prescription with multiple refills. This helps to alleviate the financial burden of purchasing EC for adolescent patients who may not always have the financial means to do so, by allowing them to utilize their health insurance for coverage of the medication. When adolescents present to the office for contraception, providers can review the need for EC prior to prescribing contraception. Best practice includes dispensing EC in the office to prevent delays in accessing EC if patients cannot present to a pharmacy soon after their office visit. Providers are encouraged to offer each type of EC in the office when able to: the levonorgestrel 150 mg tablet, the ulipristal acetate 30 mg tablet, and the copper IUD. Although the levonorgestrel tablet is effective in preventing pregnancy when utilized within 72–120 hours after unprotected vaginal intercourse, data do show that its efficacy is decreased in patients with body mass index (BMI) in the overweight and obese ranges; however, this difference in efficacy does not mean that it cannot be prescribed or dispensed to patients with overweight or obesity [21, 22]. When able, providers should dispense or prescribe the ulipristal acetate tablet, as it maintains effectiveness up to 120 hours for pregnancy prevention and is more effective in patients with elevated BMI. Some data do show, however, that ulipristal acetate's effectiveness is also somewhat decreased in patients with obesity [22]. The copper IUD can be used as EC for adolescent patients who present to the office within 5 days of unprotected intercourse, and provides an additional advantage of continued, long-term contraception, regardless of weight status [21, 22]. Providers can review Chap. 10 of this textbook for review of available emergency contraception options, including indications and prescribing considerations.

Lastly, in order to reduce provider bias and promote equity, providers should be aware of and work to integrate the Reproductive Justice framework into their contraceptive counseling of adolescents as well as adults. Reproductive Justice is a term that was coined in the 1990s by Sistersong, an organization of women of color, to bring together the reproductive rights movement with social justice. Reflecting on the reproductive health inequities that women of color both in the United States and globally have been subject to, the Reproductive Justice framework promotes not only individual reproductive rights, but equitable access for all people to reproductive health care, including abortion, contraception, comprehensive sex education, STI prevention and care, and prenatal and pregnancy care [23].

Providers should consider their own biases when providing contraception care for adolescents; and, in order to build patient–clinician trust and optimize the impact of their counseling, they should consider openly acknowledging the historical injustices around reproductive health that racial minorities have endured. Most importantly, they should ensure that the patient's priorities are driving the contraceptive choices that are made, rather than the clinician's comfort with those choices [24].

LARC for Adolescents

Both the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) recommend LARC as first-line contraception for adolescents, due to superior efficacy, ease of use, and safety [18, 25].

There are many benefits for the adolescent in using a top tier contraceptive method. These include highly effective contraception due to optimal ease of use, improved continuation rates, and the ability to use a discrete contraceptive method [18, 25]. These benefits were demonstrated by the Contraceptive Choice Project, a study conducted by researchers in St Louis, MO from 2007 to 2011, in which women of all reproductive ages were provided structured contraceptive counseling that reviewed methods in order of efficacy, and were offered all methods free of charge. The study's data showed that teen participants were amenable to using a top-tier method of contraception (an IUD or implant); those that used LARC had significantly lower rates of unplanned pregnancy and abortion than those using non-LARC methods, owing in part to much improved continuation rates [26].

Contraception and Menstrual Management for Adolescents with Disability

It is estimated that about 12% of the U.S. population has a disability, with ambulatory disability being the most common type [27]. In youth, the most common types of disability are neurocognitive or developmental, especially with the rise of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder diagnosis [27]. Developmental disabilities can also be associated with congenital and/or genetic abnormalities that can affect youth in multiple domains (mental, physical, etc.). For parents of children affected by disability, puberty can present several concerns: mobility can deteriorate with growth, hormonal changes can lead to emotional and

behavioral variability, menstruation can complicate hygiene care, and dysmenorrhea can trigger agitation and behavioral problems. Quint et al., report that patients themselves will have concerns about "body image, sexuality and how menses will affect their lives" [28]. In addition to normal menstruation, per ACOG adolescents with disabilities can experience menstrual abnormalities due to other causes, "including thyroid disease in adolescents with trisomy 21, high prolactin levels due to mood-stabilizing medications, and polycystic ovary syndrome in adolescents with seizure disorders" [29]. Providers must help families to address such concerns.

Because puberty can negatively impact the disabled adolescent and their family, parents often seek menstrual suppression to help alleviate the adolescent's symptoms and relieve parental burden [28].

Although menstrual suppression has benefits, adolescents early in puberty should be allowed to progress naturally to determine how they and their caregivers react to changes like breast development or menstruation [27]. This also allows providers to engage adolescents who have disabilities in discussions about their changing body and about sexuality and sexual safety.

Although youth with disabilities are often considered to be asexual by parents, medical providers, and school, and often do not get the needed education or anticipatory guidance about sexual health, research shows that these adolescents are indeed sexual and are more vulnerable to unsafe sexual situations.

Adolescents with physical disabilities date at the same rates as other teens, and report higher rates of dating violence (25.9% vs 8.8%). Female high school students with physical disability or with chronic medical conditions report physical coercion more than other teens (19.6% vs 9.4%). Providers can initiate conversations about sexuality and sexual health during early adolescence. The AAP and ACOG recommend private interviews with teens starting around age 12–14 [27, 29]. Discussions can begin with explaining pubertal development, and potential anatomic differences between the patient and the partner(s) they are attracted to. This can advance, based on the patient's maturity level and or interest, to discussion about types of consent, sexual intercourse, pregnancy prevention, and STI prevention. It is important to emphasize the adolescent's autonomy with respect to contraceptive choices, even for patients with mild intellectual disability (ID). For patients with more severe intellectual disability, the degree of autonomy given around contraceptive choices will depend on parental decision-making guided by the medical provider. Providers should also discuss safety with patients with physical and/or intellectual disability.

One relatively easy abuse prevention technique to teach is "NO-GO-TELL": in an uncomfortable situation, the adolescent says NO clearly, tries to GO away, then TELLs a trusted adult; families can practice this at home [27].

Menstrual management becomes a common discussion for providers caring for adolescents with physical or intellectual disability. A provider should first assess whether menses are abnormal (length, flow, frequency, associated symptoms). Some patients will need intervention to treat abnormal menstruation utilizing hormonal medications without need for both. Other adolescents will need both and others will only need contraception [27]. For patients with severe disability, caregivers may request menstrual suppression to simplify hygiene needs or to manage changes in behavior that present with menstruation (i.e., irritability or aggression). The provider should take several factors into consideration. If amenorrhea is the goal, caregivers should be aware that some hormonal methods may cause prolonged episodes of unpredictable spotting or bleeding; this may alter the patient's baseline hygiene needs/routine. Another factor to consider is that some hormonal methods are associated with weight gain, which if it occurs, can make mobility more difficult, especially for adolescents who rely on assistive devices, and thereby decrease their independence [27]. Providers should also take into consideration any comorbid conditions and/or risk of using hormonal methods. For example, some hormonal methods can increase risk of VTE, may interact with medications (e.g., antiepileptic medications), or affect bone health [27–29]. Providers should refer to the U.S. Medical Eligibility Criteria for Contraceptive Use to determine whether a contraceptive method is safe for use with any given medical condition or medication [30].

Assessing risk of venous thromboembolism (VTE) can be a difficult task. The estimated risk of VTE for the general young adult population is 2.1 in 10,000. This risk increases to 4.8 in 10,000 with use of estrogen. Other factors can increase risk of VTE including increasing age, obesity, prolonged immobility, heart failure, major surgery, or trauma [31]. Patient personal history of VTE is an absolute contraindication to estrogen-containing methods; family history of VTE must be carefully considered [30]. For those without VTE history, the various combined hormone delivery methods are each associated with variable VTE risk. Per Quint, "compared with users of COCP that contain levonorgestrel, the adjusted relative risk of venous thrombosis in users of transdermal patches was 2.3 (1.0:5.2) and of the vaginal ring was 1.9 (1.3:2.7)" [27]. It is recommended that adolescents with mobility concerns who have no other risk for VTE initiate hormonal method with 20–30 mcg ethinyl estradiol "with a first- or second-generation progestin" [27].

Adolescents with seizure disorders may benefit from the use of progestins for contraception and/or menstrual suppression.

Progestins are thought to increase seizure threshold and therefore be beneficial for patient with epilepsy [29]. Antiepileptic medications induce the hepatic cytochrome P450 system and adolescents taking these and other neuropsychiatric medications may experience altered contraceptive metabolism, which may alter contraceptive efficacy and/or lead to breakthrough bleeding [28]. Adolescents on

such medications will need contraceptive methods with higher estrogen/progestin levels, which may pose increased VTE risk. As such, the progestin-only methods are recommended for contraception and/or menstrual suppression for adolescents taking antiepileptic medications, including the hormonal IUDs, implant, injections, and progestin tablets; adolescents using depot medroxyprogesterone acetate (DMPA) may benefit from injections given every 10 weeks rather than 12 weeks to decrease irregular bleeding [29]. Of note, although antiepileptic medications are not typically altered by hormonal contraceptives, lamotrigine efficacy can decrease when given with combined oral contraceptive pills, and its dosing will need to be increased by the prescribing provider in order to maintain seizure prevention [28].

When prescribing a hormonal method for contraception and/or menstrual suppression in an adolescent with disability, families and patients may trial several methods before finding the one that most suits their needs or goals. Such goals may include amenorrhea or less frequent menses in order to enable patients to participate in their normal activities, and providers can reassess at follow up visits to determine if those goals have been met [28]. The most common methods for menstrual suppression reported by Quint et al. were "the extended or continuous oral contraceptive (COC) pill (42.3%), followed by the patch (20%), expectant management (14.9%), DMPA (11.6%), and the levonorgestrel intrauterine device (2.8%)" [28]. The use of COC pills can lead to optimal suppression of menses when used continuously. Adolescents may experience unscheduled bleeding at first, but 50% of patients eventually achieve amenorrhea [28]. Regarding administration, a chewable COC pill is available for adolescents who cannot swallow tablets, or parents can crush COC pills to administer. Progestin-only tablets, such as the "mini-pill" can achieve menstrual suppression, but this is dependent on on-time daily dosing; other higher dose progestins, such as norethindrone acetate and medroxyprogesterone acetate can be used as well [28, 29]. The combined hormonal contraceptive patch is a good alternative for adolescents who cannot swallow tablets. The patch can be used cyclically or with continuous dosing to achieve less frequent menstruation. Parents who choose the patch for their teen should place it high on the back or on the buttock to prevent their adolescent with developmental disability from removing the patch. The combination hormonal contraceptive ring may be a good option for adolescents with mild developmental delay or without mobility issues (including limited hand motility), but intravaginal insertion may present "clear intimacy issues with caregivers assisting with insertion of a ring." For those who are good candidates, the ring can also be used cyclically or with extended dosing to achieve menstrual suppression [27–29]. Typically, the hormonal implant is not recommended for menstrual suppression as it may require sedation for an adolescent with intellectual disability and has a high risk of prolonged breakthrough bleeding [29].

The DMPA injection is available as an intramuscular or subcutaneous injection. Providers should be aware that DMPA can also be given as subcutaneous injection. This alternative administration route may be more advantageous for adolescents with disability with additional medical conditions such as bleeding disorders or thrombocytopenia, as intramuscular injection can lead to hematoma formation for

such patients. The menstrual suppression rate with DMPA is "50% to 60% at year 1 and 80% at year 5" [28]. However, the use of DMPA in adolescents with disabilities raises two main concerns. The first is weight gain, which according to the prescribing information is an average of 13.8 pounds with 4 years of use [28]. Potential weight gain is a more significant concern for adolescents who already have elevated weight or obesity, since exacerbations can further limit mobility and increase dependence on caregivers. The second concern is fracture risk [28]. Bone density accrual is accelerated during puberty and the process is slowed with DMPA use in typical adolescents. Fortunately, studies demonstrate that bone density recovers when DMPA is discontinued. Providers should be aware that bone mineral density is lower in adolescents with disabilities and limited mobility. DMPA use in adolescents with disability does not necessarily lead to increased fracture risk; their bone mineral density also recovers with discontinuation [28, 29].

The hormonal IUD can be used for menstrual suppression in adolescents with disabilities. This method will lighten menstrual bleeding over time and can lead to partial or complete amenorrhea. Of the four available hormonal IUDs, the 5-year 52-mg levonorgestrel IUD presents a higher likelihood of amenorrhea [29]. IUD insertion under sedation can be considered for adolescents with disabilities with "nulligravid status, unpredictable cooperation, a narrow vagina, and significant contractures" [29]. An additional consideration is that nonverbal adolescents with decreased levels of pelvic sensation might not be able to describe discomfort and pain once the IUD is in place, which could otherwise indicate malposition, expulsion, or perforation. There are several studies addressing the use of IUDs in adolescents with intellectual disability and they report, on a total of 105 patients, a rate of 70% (28 of 40) with amenorrhea, expulsion rate of 8.5% (6 of 70), and removal for bleeding or pain of 5.7% (4 of 70) [27].

Contraception for Adolescents with Chronic Medical Problems

Adolescents with chronic medical conditions must also be considered carefully. Though they are also often thought by their pediatric medical providers, as well as families, to be less sexually active than their healthy counterparts, they may in fact be at higher risk for certain potentially risky behaviors such as early sexual intercourse [32].

Young women affected by medical conditions such as cystic fibrosis, type 1 diabetes mellitus, congenital heart disease, or sickle cell anemia may be at higher risk for the complications of pregnancy. Additionally, they are frequently prescribed teratogenic medications for the management of their conditions [33].

Both pediatric and adult subspecialty providers have reported a lack of comfort with discussions of sexuality and contraception, leaving it up to the patient to initiate a discussion thereof, or for them to discuss such issues with their primary care or dedicated women's health provider [34, 35]. All of these factors make comprehensive sexual health education and contraceptive counseling all the more critical for adolescents with chronic disease.

As noted previously, the CDC has issued both Selected Practice Recommendations [36] and Medical Eligibility Criteria [30], which detail safety and risks associated with use of both hormonal and nonhormonal contraceptive methods across a multitude of medical conditions, as well as for different age categories. While the copper IUD and most progestin-only methods are safe for most patients, combination hormonal contraceptives that include estrogen may be contraindicated, particularly for adolescents with hypercoagulable conditions or risk for venous thromboembolism, or others such as migraine with aura, uncontrolled hypertension, or hepatic tumors. Additionally, as noted earlier, hormonal contraceptives may interact with medications such as antiepileptic drugs or with some antibiotics. Conversely, adolescents with chronic medical conditions may benefit even more than their healthy counterparts from the noncontraceptive benefits of hormonal contraceptives, given that their quality of life may already be adversely affected by their medical condition. As has been noted in previous chapters, use of hormonal contraceptives can result in significant improvements in irregular menses, heavy menstrual bleeding, dysmenorrhea, and hyperandrogenism, all of which can, in turn, improve quality of life. They may therefore be indicated for many adolescents with chronic medical conditions for these reasons as well.

For adolescents affected by eating disorders, clinicians must carefully weigh the risks and benefits of both using and not using contraceptives. While they may be amenorrheic, adolescents with anorexia nervosa (AN) may still be at risk for pregnancy, yet in a malnourished and suboptimal state of health. In these situations, contraception should certainly be recommended, and both barrier methods and the copper IUD should be considered. Hormonal contraceptives can be considered as well, but concerns exist about their possible impact on bone health, though this has been controversial [37]. Additionally, given the importance of a return to pre-illness menstrual patterns as a sign of recovery from restrictive eating disorders such as AN [38], some clinicians consider the masking effect of hormonal contraceptives to be a deterrent to use. Risk for pregnancy must therefore be weighed against the possible risks of each contraceptive on an individual basis for affected patients.

Contraception for Transgender and Gender Nonconforming Youth

Accessing sexual health services is difficult for many adolescents but can be an even greater hurdle for transgender and gender nonconforming (TGNC) adolescents. A survey completed by Lambda Legal illustrated just how difficult accessing medical

care can be for LGBT persons. Their report found that "more than half of all respondents … have experienced at least one of the following types of discrimination in care: being refused needed care; health care professionals refusing to touch them or using excessive precautions; health care professionals using harsh or abusive language; being blamed for their health status; or health care professionals being physically rough or abusive" [39]. Seventy percent of TGNC patients reported one or more such experience. When compared to LGB and HIV positive respondents, the report found that TGNC respondents experienced higher rates of discrimination. Over 50% of TNGC patients worried that they would be refused medical care they needed [40]. By being aware of the discrimination faced by patients, providers can be more culturally competent and help limit such barriers to care.

When TGNC youth access care, providers should be well versed in discussing pregnancy and HIV prevention with this vulnerable population.

Per Mehringer, "by maintaining a calm and respectful demeanor, affirming the youth's gender identity, providing support and accurate information, and taking steps to help the youth maintain a sense of dignity and control, providers may increase a transgender youth's access to high quality care, avoid causing trauma, and position them to lead a healthy sexual and reproductive life" [41]. Providers should avoid using gendered terminology while discussing a TGNC patient's history and while discussing medical recommendations. If patients are comfortable with medical terminology, it is recommended that providers use appropriate terminology for body parts when providing medical advice (i.e., vulva, vagina, menstruation, penis, and testicles); this is also paramount in educating the patient about body parts and function. The use of colloquial or vulgar terminology is not recommended as this can lead to uncomfortable situations for both the patient and provider, which can compromise professionalism and rapport. However, if a patient with gender dysphoria is visibly emotionally triggered by the use of certain terminology, providers may ask TGNC patients what terminology they use to refer to their own body parts, so that the provider can use the same terminology as the patient [41]. Providers can help patients feel more at ease during an appointment by explaining, in advance, the reasons for asking particularly sensitive questions or for performing sensitive examinations [41]. In order to provide appropriate contraceptive and reproductive counseling, providers should ask direct questions about attraction, relationships, and sexual practices.

Although fertility, as well as fertility preservation, is often discussed with providers who prescribe gender affirming hormones, TGNC adolescents may not feel they need contraception for several reasons. Some TGNC youth choose to delay sexual activity because their gender dysphoria may make it difficult for them to become intimate with a partner. Other TGNC youth choose not to pursue contraception as they do not know the options available to them and often assume providers will prescribe contraception that may affect or delay their physical transition goals. Others still may be unaware of their contraceptive needs. The contraceptive needs of TGNC youth vary depending on gender identity, the presence of reproductive organs, and the use of hormones for physical transition. For TGNC patients who are in early puberty (tanner 2–3), providers often prescribe GNRH analogues for pubertal suppression [42]. While such patients can be quite young and may not need

contraception, the effect of the GNRH analogues includes suppression of the hypothalamic–pituitary–gonadal axis with subsequent suppression of follicle stimulating hormone and luteinizing hormone production. This in effect suppresses gametogenesis, but data on contraceptive efficacy in humans is not available [41]. We recommended that providers discuss contraceptive options with all sexually active young adolescents on GNRH analogues for pubertal suppression.

TGNC youth receiving feminizing treatment with estrogen and antiandrogen medications (i.e., spironolactone) still require contraception as these medications do decrease sexual function but are not effective as contraception when used together or individually [42, 43]. Per the Center of Excellence for Transgender Health 2016 guidelines, "sexual and gonadal effects include reduction in erectile function, changes in libido, reduced absent sperm count and ejaculatory fluid, and reduced testicular size" [42]. Despite such reduction in fertility, GNC youth who engage in insertive penile-vaginal intercourse with a partner who retains ovulatory function are at risk for pregnancy. It is important for TGNC youth to engage their partners in discussions about effective contraception if they wish to prevent pregnancy. Contraceptive options for transfeminine TGNC adolescents include barrier methods, withdrawal method, vasectomy, and orchidectomy [43]. Although highly effective, surgical interventions can be difficult for minors and even young adults to access.

TGNC youth receiving masculinizing treatment with testosterone also require contraception, as testosterone does not fully suppress ovulation despite the effect of menstrual suppression [41–44]. A typical treatment goal for transmasculine TGNC patients is menstrual suppression, which the use of testosterone usually achieves after 3–6 months of continuous use [42]. Providers can help manage gender dysphoria related to menstrual suppression with use of progestins, while awaiting testosterone-induced amenorrhea to occur. For TGNC adolescents who are not in need of contraception, providers can utilize norethindrone acetate or medroxyprogesterone acetate tablets for menstrual suppression [41, 44]. "While theoretically these may function as contraceptives, there is limited available evidence and thus these formulations cannot be recommended for contraception. As these formulations contain higher doses of progestin than the mini-pill, they typically result in greater ovulatory suppression and endometrial atrophy and thus provide better effects at menstrual suppression" [41]. In order to achieve menstrual suppression, norethindrone acetate and medroxyprogesterone acetate can be titrated to an effective dose.

Discussions of family planning and contraception are necessary when caring for TGNC patients on masculinizing gender affirming hormonal treatment, not only because testosterone is insufficient for pregnancy prevention, but also because it is teratogenic [41–44]. All available contraceptive options can be discussed with transmasculine adolescents. However, estrogen containing contraceptive options, including the oral contraceptive pill, the contraceptive patch, and the contraceptive vaginal ring, are not typically recommended for patients taking testosterone for the treatment of gender dysphoria, as estrogen can counter the masculinizing effect of testosterone [43]. Additionally, many transmasculine adolescents are not interested

in taking "feminine" hormones. Estrogen containing contraception can be offered to TGNC adolescents who are not on testosterone or GNRH analogues as they "are unlikely to raise total body estrogen levels" [41]. The pill, patch, and ring can be used with extended cycle dosing to induce menstrual suppression, although many TGNC adolescents with gender dysphoria related to their genitals may find it difficult to insert the vaginal ring [41]. Another consideration is that estrogen-containing methods can cause chest/breast tenderness and discomfort that may worsen a patient's gender dysphoria [44].

The provider can recommend LARC as first line contraceptives to TGNC adolescents, as for other adolescents. Placement of the IUD in TGNC adolescents on testosterone may be more difficult, as hypoestrogenized vaginal tissue may be atrophic and more fragile; "premedication with a course of vaginal estradiol may improve atrophic vaginitis" [44].

A patient's gender dysphoria, specifically dysphoria related to genital exam, speculum placement, and pelvic manipulation may also make IUD placement difficult. Providers can offer distraction techniques (music therapy, assistance from Child Life services, etc.) or in-office sedation to facilitate IUD placement without significant trauma [44, 45]. The copper IUD is a nonhormonal contraceptive option that can be used by TGNC adolescents without interfering with testosterone treatment [43, 44]. This LARC method is highly effective for pregnancy prevention but does not provide menstrual suppression. It can be offered to TGNC patients who have achieved menstrual suppression with testosterone treatment, although unscheduled bleeding is still possible after placement [41, 43, 44]. The hormonal IUDs are an effective contraceptive option as well. The 5-year 52 mg levonorgestrel IUD achieves the same rates of lighter menstrual bleeding, breakthrough bleeding, menstrual suppression, and expulsion in TGNC on testosterone as it does for nontransgender female patients [45]. Additional benefits of the hormonal IUDs for TGNC transmasculine adolescents include protection of "the endometrium against the theoretical risk of proliferative activity induced by androgen therapy used as a part of medical transition." This may decrease risk of endometrial cancer for patients who have not had or do not want hysterectomy as part of their transition because progestin "therapy is known to antagonize estrogen's proliferative effect on the endometrium" [45].

The etonogestrel implant is another excellent contraceptive option for TGNC adolescents who have achieved amenorrhea with testosterone for treatment of gender dysphoria [41, 43, 44]. However, providers should be cautious about etonogestrel implant placement in TGNC adolescents who continue to menstruate and have significant gender dysphoria related to menstruation, as this method can cause unpredictable bleeding [41].

The DMPA injection is effective for pregnancy prevention, with a low failure rate, but this method can also cause unpredictable bleeding with initiation, reversibly affect

bone mineral density accrual, and lead to weight gain. The unpredictable bleeding pattern with implant and with DMPA can worsen a TGNC patient's gender dysphoria. Weight gain can cause gender dysphoria to worsen as well, especially if a TGNC patient has increase in chest/breast tissue with weight change. Providers should discuss these potential outcomes with patients and monitor side effects, as well as levels of dysphoria. Despite these concerns, DMPA is a "popular option for menstrual regulation among transmasculine youth because the progestin has a more androgenic effect compared to other progestins" [41]. With continued DMPA use, most TGNC patients achieve menstrual suppression and as such, DMPA is a good option for transmasculine patients, whether receiving testosterone therapy or not [41, 43, 44].

Other contraceptive options available for transmasculine TGNC adolescents who have not had or who do not want hysterectomy and/or oopherectomy include the barrier methods, as well as less reliable methods with higher risk of pregnancy, including the withdrawal method or natural family planning. Natural family planning methods are difficult for the general adult population to employ and are even more difficult for adolescents. For TGNC patients who have irregular menstruation on testosterone treatment, natural family planning methods are not recommended. Cervical caps, diaphragms, and sponges are not commonly used by adolescents and, like the vaginal ring, are not likely to be utilized by transmasculine TGNC patients. The internal condom also involves vaginal manipulation and, by the same token, may not be considered favorably by TGNC adolescents. The external condom is most likely to be employed by transmasculine TGNC who engage in vaginal intercourse.

For TGNC patients employing less effective contraceptive methods, those still considering contraception, or those with inconsistent/incorrect use of contraception, all three available types of emergency contraception can be prescribed [41, 43]. Transmasculine TGNC adolescents can achieve effective contraception with gender affirming surgical interventions with hysterectomy and/or oophorectomy, however as with transfeminine TGNC adolescents, these surgical interventions can be difficult for minors and even young adults to access.

Conclusion

Health care providers play an important role in the prevention of unintended pregnancy in adolescents, which, despite major declines in recent decades, is still a significant source of medical morbidity and suboptimal developmental and psychosocial outcomes in youth in the United States. Sensitive and well-informed sexual health history taking and counseling are critical to provision of effective contraception, and providers must ensure to include all adolescents, including those with cognitive and physical disabilities, chronic medical problems, and gender diversity, when considering their need and eligibility for contraceptive methods. LARC are recommended as first line methods for all adolescents; providers should ensure that they approach adolescent patients through a reproductive justice lens in order to ensure comprehensive, equitable, and noncoercive counseling and treatment.

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Chapter 19
Controversies in Contraception

Jessica W. Kiley, Weronika A. Armstrong, and Lee P. Shulman

Controversies in Contraception

Few areas of medical care are as fraught with controversy as female contraception. Most debates in the lay community stem from divergent political and religious standpoints, with such discussions invariably deliberating on women's rights to control their own fertility. Within the medical community, debates mostly revolve around the safety of highly effective hormonal and intrauterine methods, with such disputes being frequently used as fuel in the overarching sociopolitical deliberations. Health care providers must be familiar with the evidence behind the controversies. Women often present with preformed ideas about the safety or risks of taking certain contraceptives. These preconceptions can lead to reluctance to accept contraception and result in unintended pregnancy. This chapter presents evidence surrounding some of the major controversies in modern contraceptive care.

Breast Cancer Risk

The issue of breast cancer risk in women using hormonal birth control resonates in the medical community as well as in the lay population of women. As public awareness of breast cancer incidence increases and detection strategies evolve, patients

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and providers encounter questions regarding the appropriateness of hormonal birth control with respect to breast cancer development during the reproductive years and afterward.

Concerns over an increased breast cancer risk with use of combined oral contraceptives (COC) date back several decades. The standard opinion that current COC users have a slight increased risk of developing breast cancer during pill use resulted from findings of a sentinel 1996 publication [1]. In this meta-analysis of 54 epidemiologic studies, 53,000 women with breast cancer were compared with 100,000 women without breast cancer. Women using COC were more likely to be diagnosed with breast cancer, with a relative risk (RR) of 1.24 (95% confidence interval [CI], 1.15–1.33). The populations in these studies used older COC formulations, many of which contained considerably higher estrogen and progestin doses. Subsequent studies including women using modern COCs have demonstrated no association between pill use and an increased breast cancer risk. In one study, a cohort of 259,956 women in Shanghai was followed for up to 10 years. The relative risk for breast cancer incidence in COC users was 0.90 (95% CI, 0.78–1.03) [2]. Similar results were found in a study of 4575 women with breast cancer compared with 4682 controls. History of COC use was assessed by interview. The relative risk of developing breast cancer was 1.0 (95% CI, 0.8–1.3) for current COC users and 0.9 (95% CI, 0.8–1.0) for past users. The relative risk did not increase consistently with longer duration of use or with higher doses of estrogen [3]. A third study found that breast cancer mortality in COC users and nonusers was similar in a cohort of 17,032 women followed for up to several decades. There again was no association between ever-use of COCs and mortality from breast cancer (RR 1.0, 95% CI, 0.8–1.2), and fatal breast cancer was unrelated to length of exposure to COCs [4]. A 2017 study reported on the associations between modern hormonal contraceptive use and breast cancer incidence in 1.8 million women in Denmark, between 1995 and 2012. The relative risk of breast cancer in hormonal contraceptive users, compared with nonusers was 1.20 (95% CI, 1.14–1.26). Longer duration of use was associated with increased RR. The RR with less than 1 year of use was 1.09 (95% CI, 0.96–1.23) and 1.39 (95% CI, 1.26–1.51) with use longer than 10 years [5].

It is unclear if progestin-only contraceptives affect breast cancer incidence, and any increase in breast cancer risk is likely of small magnitude [6]. No increased risk of breast cancer is shown in users of injectable and implantable progestin contraceptives [7, 8]. The 2017 Danish study reported a higher risk of breast cancer in women using the levonorgestrel intrauterine system (LNG-IUS), compared with women who had never used hormonal contraceptives (RR 1.21, 95% CI, 1.11–1.33) [5]. Previously, no increased rate of breast cancer was reported in women using the LNG-IUS [9, 10].

Taking these data as whole, it is reasonable to conclude that the available evidence suggests a small increase in breast cancer incidence in hormonal contraceptive users, but the absolute risk of breast cancer remains low. It is uncertain if this increase is a direct effect of hormone exposure or if contraceptive users are more likely to have their cancers detected sooner, or a combination of factors [11].

Clinicians should counsel women about the risks of benefits of the various hormonal and nonhormonal contraceptive methods to allow an informed choice. Furthermore, women should understand ways to reduce breast cancer risk, such as improved nutrition and exercise [12].

BRCA Carriers

Women who carry *BRCA1* or *BRCA2* mutations are at increased risk of developing breast and ovarian cancers. These women have an estimated 65–75% lifetime risk of breast cancer. The risks of ovarian cancer are 40 and 20%, respectively, in *BRCA1* and *BRCA2* carriers [13, 14]. The effect of hormonal contraception on breast cancer incidence in these women is not entirely clear, but the available evidence suggests that COC use in *BRCA1* and *2* mutation carriers is unlikely to modify breast cancer risk [15–17].

Conversely, studies evaluating COC use and risk for ovarian cancer consistently support a risk-reducing effect on ovarian cancer with COC use. A collaborative analysis of 45 epidemiological studies reports a 27% risk reduction with ever-use of COC, in 23,000 ovarian cancer cases and 87,000 controls. Greater risk reduction was demonstrated with longer duration of COC use. While prophylactic bilateral salpingo-oophorectomy (or bilateral salpingectomy alone) is the primary approach for ovarian cancer risk reduction in *BRCA1* and *2* mutation carriers, COC use in carriers who do not undergo surgery is associated with a lowered risk of developing ovarian cancer [18, 19].

A 2011 meta-analysis demonstrated mixed results for breast cancer risk *BRCA1/2* carriers using COCs. In case-control studies, breast cancer risk was not associated with COC use in *BRCA1* (odds ratio [OR], 1.08; $p = 0.250$) or *BRCA2* (OR, 1.03; $p = 0.788$) carriers. In contrast, a subset of cohort studies showed a significantly increased risk of breast cancer in *BRCA1* mutation carriers using COCs (RR, 1.48; 95% CI, 1.14–1.92). This study also reported a reduced risk of ovarian cancer in

BRCA1/2 carriers with any past COC use (OR, 0.57; 95% CI, 0.47–0.70; $p < 0.001$) and a significant downward trend with increasing duration of COC use (OR, 0.95; 95% CI, 0.93–0.97; $p < 0.001$) [20].

A subsequent meta-analysis in 2013 found that the associations between COC use and breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers follow the same patterns seen in the general population. Meta-analysis showed an inverse association between COC use and ovarian cancer risk (OR, 0.58; 95% CI, 0.46–0.73) for *BRCA1/2* carriers combined, and no association with breast cancer (OR, 1.21; 95% CI, 0.93–1.58). When *BRCA1* and *BRCA2* mutation carriers were analyzed separately, findings were similar [21].

Women with a Family History of Breast Cancer

Women whose family members are affected with breast cancer are at higher risk of breast cancer than women with no family history. Consistent with findings for the general population and for *BRCA1/2* mutation carriers, hormonal contraceptives do not appear to increase breast cancer risk in these women. The Centers for Disease Control's Medical Eligibility Criteria for Contraceptive Use (CDC MEC) assigns a category 1 rating to all hormonal and nonhormonal contraceptive methods in women with a family history of breast cancer, meaning that there is no restriction for use of any method in this population [22].

Contraception in Women with a Personal History of Breast Cancer

Women currently undergoing treatment for breast cancer are not candidates for hormonal contraceptives, since breast cancers are hormonally sensitive. Indeed, hormonal contraceptive use could worsen cancer prognosis. The progestin- and estrogen-receptor status of the tumor may impact breast cancer recurrence with hormone exposure. There is at least theoretical concern that progestin receptor-positive cancers are more likely to recur with use of progestin-containing contraceptives.

Hormonal contraception is relatively contraindicated in women who have undergone breast cancer therapy and are free of disease for at least 5 years. The CDC MEC assigns a category 3 rating to all combined and progestin-only contraceptive methods for such women [22].

It should be noted that there is a dearth of data in support of this restriction on LNG-IUS use, as the issue has not been well studied.

One study evaluated breast cancer recurrence in LNG-IUS users and nonusers and found no difference between groups, with an adjusted hazard ratio of 1.86 (95% CI, 0.86–4.00). Breast cancer recurrence was detected in 17 of 79 LNG-IUS users (21.5%), compared with 20 of 120 nonusers (16.6%). An additional subgroup analysis found that women who used the LNG-IUS at the time of diagnosis and continued its use had higher rates of recurrence than those who discontinued use (adjusted hazard ratio 3.39; 95% CI, 1.01–11.35). These data must be interpreted with caution based on the small sample size, study design, and finding of borderline statistical significance [23].

The effects of progestin released from the LNG-IUS on normal breast tissue are largely unknown; and the role of progestins overall in the pathogenesis of breast cancer is unclear. Based on the available evidence, women with a personal history of breast cancer, either current or past, are best served by using nonhormonal contraception. Based on their superior effectiveness over barrier methods, the copper intrauterine device or tubal sterilization should be considered as first-line options for such women.

Venous Thromboembolism

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism. VTE is a life-threatening condition, with a yearly incidence of 300,000–600,000 cases in the United States [24, 25]. Extensive research has explored the relationship between hormonal contraception and VTE, with estrogens and progestins both being implicated in the increased risk for VTE among combined hormonal contraceptive users.

> While the relationship between estrogen and VTE risk is generally accepted, the association between progestins and VTE remains controversial. These rates must be considered in the context of the risk of VTE associated with normal pregnancy as discussed below.

Estrogen increases the risk of VTE in a dose-dependent fashion, particularly among patients using COCs containing 50 mcg or more of ethinyl estradiol (EE) [26]. The incidence of VTE in women aged 15–44 not using COCs is 5–10 per 100,000 woman-years. Women taking low-dose COCs experience VTE at a rate of 12–20 cases per 100,000 woman-years. The rate increases to 24–50 cases per 100,000 woman-years with higher dose preparations. These rates must be considered in the context of the risk of VTE associated with normal pregnancy, which further increases the rate to 60 cases per 100,000 woman-years [27].

Debate continues to surround the impact of progestin type on VTE risk. Various progestin types may have differing effects, but the magnitude of these differences is

rather small, and the clinical relevance of these differences is likely minimal. In the mid-1990s, analysis of data suggested an association between third-generation progestins and an increased occurrence of thromboembolic events. In COC nonusers aged 20–24, the incidence of VTE was estimated at 3 events per 100,000 women per year. The risk rose to approximately 9 per 100,000 woman-years for users of pills with second-generation progestins, and increased to as high as 21 per 100,000 woman-years in users of pills containing desogestrel or gestodene. Studies comparing rates of VTE among users of pills containing levonorgestrel versus those containing either gestodene or desogestrel demonstrated a relative risk for VTE of 1.3–2.2 [26]. These data were mostly derived from large case-control studies and resulted in the "Pill Scare" of 1995, a time when many women discontinued their COCs after hearing media reports of higher rates of potentially fatal thromboembolic complications. As a result, many parts of Europe documented considerably increased rates of unintended pregnancy and abortion during the same time period [27].

Studies implicating desogestrel and gestodene as "higher risk" progestins suffered from user bias and inconsistent methods used to diagnose VTE among subjects. Subsequent case-control studies, which attempted to adjust for bias and confounding variables, showed no increase in VTE risk with third-generation progestins. Conversely, two separate meta-analyses again demonstrated a higher risk of VTE with a relative risk of 1.5–2. Some newer data suggest that COC-related VTE rates increase within the first year of use and decrease thereafter. Overall, the absolute risk of VTE remains low given the very low incidence of VTE in patients without other significant risk factors [26]. The risk is acceptable to most patients and clinicians and is profoundly lower than the risk of VTE associated with pregnancy and the postpartum period.

Interestingly, a decade and a half after the "Pill Scare," reports of increased VTE risk with another new progestin emerged. Two large European studies reported higher rates of VTE in women using COCs containing drospirenone compared with those containing levonorgestrel. In a large cohort study, risk ratios for VTE in women using COCs containing desogestrel 1.82 (95% CI, 1.49–2.22), with gestodene 1.86 (95% CI, 1.59–2.18), and drospirenone 1.64 (95% CI, 1.27–2.10) were documented, compared with levonorgestrel-containing pills [28]. The second study was a case-control study reporting odds ratios of 3.6 (95% CI, 2.9–4.6) in levonorgestrel-containing pill users, compared with nonusers. The odds ratio was 6.3 (95% CI, 2.9–13.7) for pills containing drospirenone, 5.6 (95% CI, 3.7–8.4) for gestodene, and 7.3 (95% CI, 5.3–10.0) for desogestrel [29]. These studies were roundly criticized for profound methodological limitations, including misclassification of VTE, inadequate control of confounding variables and other sources of bias [30].

Upon review of the data on drospirenone and VTE, the US Food and Drug Administration (FDA) issued a statement that COCs containing drospirenone *may* be associated with a higher risk of blood clots than COCs containing other progestins. However, causality was not shown, since the reviewed studies were heterogeneous in nature, failed to control for variables such as smoking and body mass index, and because the studies reported inconsistent estimates of the risk of VTE in drospirenone-containing pills compared with other COCs [31].

Subsequently, two case-control studies published in the same issue of one journal reported increased VTE risks in drospirenone-containing pills compared with levonorgestrel formulations. In one study, based in the United States, data were ascertained from billing claims, and 183 women with idiopathic VTE (VTE in the absence of other risk factors) were compared with 681 controls. The incidence rates for VTE in drospirenone pill users was 30.8 (95% CI, 25.6–36.8) per 100,000 woman-years and 12.5 (9.61–15.9) per 100,000 woman-years for levonorgestrel pill users. The age-adjusted incidence rate ratio for VTE was 2.8 (95% CI, 2.1–3.8) for current users of COCs containing drospirenone compared with those containing levonorgestrel [32]. The other study used registry data in the United Kingdom, and following similar methods; 61 cases were compared with 215 matched controls. The crude incidence rate of VTE was 23.0 (95% CI, 13.4–36.9) per 100,000 woman-years in current users of COCs containing drospirenone/EE 30 mcg, and 9.1 (95% CI, 6.6–12.2) per 100,000 woman-years in current users of COCs containing levonorgestrel/EE 30 mcg. The age-adjusted incidence rate ratio was 2.7 (95% CI, 1.5–4.7) [33]. These reports were criticized for inadequate control of bias.

Thrombophilia and Hormonal Contraception

Hereditary thrombophilias clearly increase the risk of VTE, but the clinical relevance of these mutations among users of COCs remains unclear. Routine screening is neither cost-effective nor clinically warranted and should not be offered except to women with a personal or family history of blood clots and those with a known familial gene mutation [34–37].

A 2006 meta-analysis reviewed 16 case-control studies of COC use in patients with inherited hypercoagulable states. Eleven studies evaluated Factor V Leiden

mutation, six studied the prothrombin gene mutation, three assessed both Factor V Leiden and prothrombin gene mutation, and three studied other mutations. COC users with the Factor V Leiden mutation have an increased risk of VTE, with odds ratios ranging from 6.4 to 99 in the literature. It remains unclear how heterozygosity versus homozygosity influences risk, and most carriers do not experience VTE when using hormonal contraceptives The Expert Working Group of the World Health Organization (WHO) recommends avoiding COCs among women known to carry the mutation. However, it simultaneously cautions against universal screening for thrombogenic mutations prior to initiating COCs. Such a practice would withhold oral contraception from 3% to 6% of women, 99.9% of whom would never develop VTE [38]. The recommendation against universal screening is similarly endorsed by the Royal College of Obstetricians and Gynaecologists [39] and the American College of Obstetricians and Gynecologists (ACOG) [40].

Bone Density

Progestin effects on bone mineral density are another source of intensely debated controversy, with implications for the clinical management of thousands of women. Concerns about bone loss with use of depot medroxyprogesterone acetate (DMPA) changed practice patterns and caused withholding of this highly effective contraception from many eligible candidates.

DMPA is a three-month injectable progestin-only contraceptive that is used by over two million women in the United States [41]. Women enjoy the convenience of quarterly dosing and non-contraceptive benefits including amenorrhea. Additionally, DMPA is an excellent option for patients with contraindications to estrogen-containing contraceptives. The mechanism of action of DMPA is inhibition of gonadotropin secretion, with prevention of follicular maturation and ovulation and thinning of the endometrium along with thickening of the cervical mucus [42, 43].

Concerns that DMPA-induced bone loss might lead to bone mineral density loss and subsequently increase the risk of fractures gained the attention of clinicians and patients alike, mostly as result of studies reporting reduced bone mineral densities in current DMPA users. Researchers hypothesized that inhibition of gonadotropin secretion also results in suppression of ovarian estradiol production, and the decreased circulating estradiol would lead to excessive bone resorption and less bone formation. Special populations of concern included adolescents and perimenopausal women—young women who had not yet achieved peak bone mass and older women who had begun to lose bone mass [41, 44].

In November 2004, the FDA issued a “black box” warning to be placed on the DMPA package labeling that stated, “Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. Depo-Provera

contraceptive injection should be used as a long-term birth control method (e.g., longer than 2 years) only if other birth control methods are inadequate." This warning led some clinicians and women to believe that DMPA was only appropriate for short-term use, requiring discontinuation after 2 years. The FDA warning was based on post hoc analyses of data from clinical trials that indicated that the degree of bone mineral density reduction at the hip (total) and femoral neck were greater than decreases at the lumbar spine in adolescents with DMPA use for more than 2 years, and that this decrease occurs at an age when individuals normally experience a significant increase in bone mass. Also, there appeared to be a lack of complete recovery of BMD at the hip at 5 years following 2 or more years of DMPA use. These findings were based on a small sample size of less than 50 adolescents [45]. In addition, the language incorporated by the FDA regarding the bone density warning for DMPA was not based on any evidence from robust clinical trials that DMPA users, either short or long term, were at an increased risk for bone fractures in users compared to nonusers.

The impact on practice patterns after the FDA mandate was researched in a survey study of Florida obstetrician-gynecologists. Using a mailed survey, physicians were asked to describe their prescribing practices for DMPA before and after the FDA requirement was enacted. Nearly half (46%) of respondents indicated that they place a time limit on DMPA use, and 66% stated that this limit was based on the FDA black box warning; 65% of physicians ordered bone mineral density testing in DMPA users, with 58% indicating that this practice was based on the black box warning [46].

In appraising the data on DMPA and its effects on bone health, clinicians must recognize that the only relevant clinical endpoint is the occurrence of fracture. Use of dual-energy X-ray absorptiometry (DEXA) assessments—while commonplace in clinical practice for bone density evaluation in postmenopausal women—is a marker without clear correlation to fracture risk in premenopausal women, especially young adult women, on DMPA or in any other clinical screening setting. DEXA has not been validated as a marker of fracture risk in teens. Observational studies on the association between DMPA and fracture risk have been limited in generalizability, prone to problems of selection bias, and inadequately controlled for confounders. One example is a US study comparing fracture rates in women with developmental disabilities using DMPA or antiepileptic medications. The study found a 2.4 times increased odds of fracture in DMPA users; but generalizability was limited due to the specific population being studied [47].

The bulk of data is derived from observational studies performed in other countries, which provide mixed results on the association between DMPA and subsequent fracture. One case-control study using the UK General Practice Research Database found an increased risk of fracture among women that were current DMPA users, compared to nonusers (OR, 1.36; 95% CI, 1.15–1.60; for women with 3–9 DMPA prescriptions and OR, 1.54; 95% CI, 1.33–1.78 for women with 10 or more DMPA prescriptions). However, when women with fractures potentially related to osteoporosis were analyzed, the risk of fracture for DMPA users (10 or more prescriptions of DMPA) was similar to that of nonusers (OR, 1.49; 95% CI, 0.97–2.28)

[48]. A second group performed a cohort study, also using the UK General Practice Research Database, finding that DMPA users had more fractures than nonusers, with an incidence rate ratio of 1.37 (95% CI, 1.29–1.45). However, DMPA users had a higher incidence of previous fracture risk than nonusers prior to contraceptive initiation, suggesting that the higher fracture risk may result from differences in fracture risk unrelated to DMPA use [49]. In a third study, women in Denmark who had experienced a fracture were compared with age-matched controls. Use of DMPA was associated with an increased risk of fracture (OR, 1.44; 95% CI, 1.01–2.06), but the number of DMPA users was small (n = 163), and variables including smoking and body mass index were uncontrolled. The findings in these studies suggest potential for a slight increased risk of fracture in DMPA users, but caution must again be taken when applying the results of registry data and retrospective observational data to clinical practice, as result of obvious problems with study design and uncontrollable biases.

Researchers have mostly used DEXA assessments as the primary outcome variable in studies on DMPA and bone loss. Reports suggest bone mineral density losses of 0.5–3.5% and the spine and hip after 1 year of DMPA use, 5.7–7.5% loss after 2 years' use, and 5.2–5.4% loss after 5 years' use [45]. The bone loss is seen during current DMPA use, and available evidence supports recovery of these losses after discontinuation of use. The time required for recovery was dependent on the duration of DMPA use, with reversibility occurring more slowly in women using DMPA for more than 2 and 3 years, compared with women using DMPA for less than 1 year. The estimated time to full recovery is about 27–30 months after discontinuation [50, 51].

Changes in bone density attributable to DMPA use were further delineated in a cohort study of 248 DMPA users and 360 women using nonhormonal contraception. After 240 weeks of exposure, bone mineral density in DMPA users had decreased from baseline by −5.16% (SD, 3.60%) in the total hip and by −5.38% (SD, 3.57) in the lumbar spine. Little change in bone density was detected in the nonhormonal contraceptive users. At all time-points during the treatment period, the decreases from baseline in the DMPA group were significantly greater ($p < 0.001$) than in the nonhormonal group. After discontinuation of DMPA, recovery of BMD toward baseline values was seen. Ninety-six weeks after discontinuation, the mean percentage change from baseline was −0.20% (SD, 3.41%) for total hip and − 1.19% (SD, 3.88%) for lumbar spine bone mineral density. Since follow-up did not extend beyond 2 years, the interval required for full recovery of bone density was not determined. Six women in the DMPA group (2.6%) and eight women in the control group (2.2%) experienced a fracture during treatment. During the post-treatment follow-up period, one woman in the DMPA group (0.8%) and two controls (1.2%) had fractures [52].

To examine bone density changes in adolescents, one study followed 98 young women aged 12–18 years for up to 240 weeks of DMPA exposure and 300 weeks after discontinuation. Bone mineral density at the time of the final DMPA dose had declined 2.7% at the lumbar spine, 4.7% at the total hip, and 3.9% at the femoral neck ($p < 0.001$). Within 60 weeks of discontinuation, lumbar spine bone mineral

density had returned to baseline values, and 240 weeks after discontinuation, it was 4.7% above baseline. Values at the total hip and femoral neck recovered to baseline 240 and 180 weeks, respectively, after DMPA discontinuation [53].

In 2005, the WHO assembled an expert panel to assess the effects of hormonal contraceptives on bone health [54]. After evaluating extensive data on bone mineral density changes related to DMPA use, the panel concluded that there should be no restriction on the use of DMPA, or on the duration of its use, in women aged 18–45 years. They also stated that in girls younger than 18 years and women over 45 years, the advantages of DMPA use typically outweigh the theoretical concern for fracture. On a worldwide scale, withholding DMPA from eligible candidates would increase the risk of unintended pregnancy, with major public health implications.

> The ACOG recently addressed recommendations for DMPA provision. Based on review of the available data and consideration of the negative public health impact of restricted DMPA use, ACOG stated in a 2014 Committee Opinion, "(T)he effect of DMPA on BMD and potential fracture risk should not prevent practitioners from prescribing DMPA or continuing use beyond 2 years. The potential health risks associated with the bone effects of DMPA must be balanced against a woman's likelihood of pregnancy using other methods or no method, and the known negative health and social consequences associated with unintended pregnancy, particularly among adolescents."

Health care providers should inform women and adolescents considering initiating DMPA or continuing to use the method about the benefits and the risks of DMPA and should discuss the US Food and Drug Administration "black box" warning and use clinical judgment to assess appropriateness of use. It is specifically noted that the medical literature lacks high-quality data addressing fracture risk later in life in women previously using DMPA. Additionally, the routine use of DEXA for monitoring changes in bone mineral density is not recommended in young women [45].

Infertility

Intrauterine Contraception and Tubal Infertility

For many years, and even now, health care providers, patients, and policy makers have believed that the presence of an IUD allows infectious organisms to ascend the genital tract and increase the risk of infection and infertility. Of the modern contraceptive methods, the IUD is the most commonly blamed for increasing the risk of subsequent infertility. This alleged association is predominantly historical, resulting from experiences with older IUD types widely used in the United States in the

1970s. The Dalkon Shield was introduced in 1970, and high rates of upper genital tract infection and pelvic inflammatory disease (PID) were documented within a few years of its release. The source of ascending infection was the IUD string, which was composed of a multifilament fiber allowing pathogenic bacteria to rise in the genital tract. Subsequently, due to media attention and fear among women and their health care providers that PID and subsequent infertility would occur, IUD use plummeted [55]. The United States has never recovered from the impact of this complication related to a device that has long since been removed from the market.

Modern IUDs and subdermal implants are the most effective reversible contraceptives, and the medical community must move beyond the "ancient" myths and work to increase IUD uptake in American women. The currently available IUDs offer long-acting reversible contraception with few side effects. In the United States in 2010, there were 2.1 million IUD users; 5.6% of all women using contraceptives chose the IUD [56], and the IUD is the most common reversible contraceptive method used by women worldwide [57]. In 2014, 4.5 million women in the United States used the IUD [58]. Recent efforts in the United States have focused on encouraging LARC use through evidence-based education of providers and the public. These efforts to dispel myths and encourage LARC use have increased LARC uptake. Although overall contraceptive use among reproductive-age women has not changed, the proportion of LARC users has risen. LARC use increased from 6% in 2008 to 14% of total contraceptive users in 2014 [59].

High-quality data evaluating the association between modern IUD use and pelvic infection show that IUD users are not at increased risk of PID or infertility.

Early literature did suggest an increased risk of PID, as high as 60% above baseline, but reanalyses of these data sets led to subsequent studies that debunked the findings of the earlier studies. Two studies in the 1980s suggested increased rates of infertility in women who had previously used Dalkon Shields, or plastic or copper IUDs [60, 61]. These studies were limited by survey methodology and recall bias, and several subsequent studies sought to define the relationship between IUDs and the tubal infertility. Unclear associations resulted from these reports, until a classic 2001 study demonstrated no increase in tubal infertility attributable to copper IUD use; 358 nulligravid women with documented tubal infertility were compared with 953 nulligravid women with infertility due to other causes, and 584 primigravid women. Participants were tested for antibodies to *Chlamydia trachomatis*, a common pathogen associated with tubal infertility. When women with tubal infertility were compared to the infertile controls, the odds ratio for tubal blockage associated with a history of copper IUD use was 1.0 (95% CI, 0.6–1.7). When they were compared with the pregnant controls, the odds ratio was 0.9 (9% CI, 0.5–1.6). Women who had not used an IUD but tested positive for antibodies to Chlamydia were more often found to have tubal infertility, when compared to pregnant controls, with odds

ratio 2.4 (95% CI, 1.7–3.2). This study provided robust evidence that the copper IUD was not associated with tubal infertility [62].

Several published studies report high pregnancy rates after IUD removal. While study designs and follow-up periods varied between studies, pregnancy rates ranged from 92 to 100%, mostly within 3 years after IUD removal [63–71]. The IUD types studied included different copper IUDs, plastic devices, and LNG-IUS models. In women who discontinued copper IUD or LNG-IUS use in order to achieve pregnancy, median times to pregnancy were short (2–4 months) [64, 67, 68, 72–75].

A recent meta-analysis reported on pregnancy rates over 12 months after contraceptive discontinuation. The pool included 14,884 women, with 2374 discontinuing an IUD. Results demonstrated an 85% return to fertility among IUD users, not significantly different from rates of other methods of hormonal contraceptives. At 12 months of follow-up, pregnancy rates after discontinuation of any contraceptive were similar to those in contraceptive nonusers [76].

When considering reversibility of contraception and subsequent pregnancy, factors such as age, lifestyle measures, and environmental variables must be considered. In counseling patients about the impact of IUD use and subsequent pregnancy, clinicians should include discussion of these factors and other preconception issues, and provide explanation of the evidence that return to fertility is generally rapid in IUD users.

Other Contraceptives and Return to Fertility

Similar to the case with IUDs, women using COCs experience rapid return to fertility and successfully conceive shortly after contraceptive discontinuation. Older data examining the time intervals between cessations of COCs and conception reported delays of months to years, but the COC formulations included in these studies were older, higher dosed products. Additionally, many older reports do not account for variables such as duration of use, age, baseline sub-fertility, or parity [55].

Modern low-dose pills do not appear to impact subsequent fertility. In a large, prospective cohort study following 59,510 COC users, 79.4% (95% CI, 77.6–81.1%) were pregnant within 1 year of stopping COCs, and 21.2% (95% CI, 19.4–23.0%) conceived one cycle after discontinuation [77]. Other recent studies report similar findings, with 1-year pregnancy rates of 79–95% and median times to conception of 2.5–3 months [72, 78].

Progestin implant contraceptives are also associated with rapid resumption of menses and return of fertility.

Studies assessing pregnancy rates after removal of levonorgestrel subdermal implants (Norplant and Norplant II) report 1-year pregnancy rates of 73–86%, and median time to pregnancy of 2.9–4.4 months. Data on the etonogestrel implant (Implanon®, Nexplanon®, Whitehouse Station, NJ) demonstrate resumption of regular menses within 3 months of removal, ovulation within the first few weeks after removal, and subsequent pregnancy rates consistent with the rates of pregnancy in the general population [79].

DMPA and Resumption of Ovulation

Of all hormonal contraceptives, DMPA is the only one that imparts a clinically significant lag in resumption of ovulation and fertility. Once fertility returns, pregnancy outcomes are similar to those in the general population.

In contrast to the case with other contraceptives, the controversy around DMPA and subsequent fertility focuses not on the ability to conceive after discontinuation, but on the risk of unintended pregnancy if a woman presents after her scheduled dosing date. It is fairly well accepted that pregnancy rates in the first year after intentional discontinuation of DMPA are lower than those with other hormonal contraceptives.

The argument concerning DMPA and return to fertility is important for service provision as women may frequently miss their scheduled 3-month redosing visit. Clinicians may withhold a repeat DMPA injection if a woman presents late for her injection, out of concern that she is already pregnant. A large number of studies have assessed the time interval until ovulation or pregnancy rates after DMPA discontinuation. Pharmacokinetic studies report that the first ovulation occurs mostly between 20 and 26 weeks after the last injection, although ovulation was seen as early as 13 weeks postinjection in a few women [80]. In most of these study protocols, ovulation resumption was measured after a single injection of DMPA [81–87]. The delay of ovulation in women using DMPA for longer periods of time is likely longer.

One small study examined return of menses after 1–2 years of DMPA use and reported that the time to ovulation was 20.4–35.6 weeks after the last injection [88]. Overall, these reports provide mixed data on resumption of ovulation, but they do not give information on the clinically significant endpoint of pregnancy risk after a missed or delayed dose of DMPA.

In a prospective cohort study of 2290 DMPA users, pregnancy rates per 100 women-years were 0.6 (95% CI, 0.33–0.92) within 13 weeks of the previous dose, 0.0 (95% CI, 0–1.88) at 13–15 weeks, and 0.4 (95% CI, 0.01–2.29) at 13–17 weeks [89].

Trials that assess pregnancy rates after DMPA discontinuation suggest low pregnancy rates in the initial period after discontinuation. These trials provide evidence that short-term pregnancy rates after DMPA discontinuation are low [90, 91], and that women can safely receive DMPA even if weeks late for their scheduled injection.

The CDC's 2013 Selected Practice Recommendations for Contraceptive Use defines the dosing interval for DMPA as 13 weeks, and gives a "grace period" of 2 weeks (15 weeks from previous injection) for reinjection without use of a backup contraceptive method [92].

The WHO supports a longer grace period of 4 weeks as low pregnancy rates exist during these time periods. The differing recommendations from the CDC and WHO are based on data from a single study reporting very low pregnancy rates, but which included a large number of lactating women. In interpreting this study, the CDC remarked that the contraceptive effect of breast-feeding could not be removed, and issued the more cautious recommendation of the 2-week grace period, or a dosing interval of up to 15 weeks between injections [92].

Weight Gain

Patients and providers alike often associate weight gain with use of hormonal birth control. A frequent patient concern when considering a new contraceptive method is its effect on weight. In contraceptive trials, weight gain is a commonly cited reason for method discontinuation. In clinical settings, women often express fear over weight gain with the initiation of oral contraceptives or other hormonal methods, and may be reluctant to start a prescribed method.

An important aspect of patient counseling when prescribing hormonal contraception is to address any concern they may have of possible weight gain with the method so as to improve compliance and patient satisfaction with the method.

Combined Hormonal Methods and Weight Change

Concern about weight gain may dissuade women from the use of effective hormonal contraception, impairing initiation of use and causing early discontinuation among users.

In one report, 75% of female survey respondents in the United Kingdom believed that COC use results in weight gain [93]. Another survey of United States adolescents reported that 45% believed weight gain was a side effect of COCs [94]. Other studies show that approximately 30% of past COC users report that they gained weight while taking the pill [95, 96]. However, a causal association between estrogen–progestin contraceptives and weight gain has not been established.

A large number of observational studies and clinical trials have examined weight gain in COC users. The vast majority document little or no weight gain in COC users, either when followed over time, or when compared to controls or users of other hormonal or nonhormonal contraceptive methods [97–99]. Studies suggesting weight increases demonstrated weight gain of a small magnitude, less than 2 kg per year [99].

A 2014 Cochrane Review reported the results of 49 trials comparing weight gain in combined hormonal contraceptive users with another hormonal contraceptive method, or with placebo or no hormonal method. A variety of COC formulations, the vaginal ring, and the transdermal patch were included in the reviewed trials. The comparisons of a combination contraceptive with a placebo or no hormonal method revealed no significant differences in weight change [100]. These included only five comparisons between a COC and a placebo [101, 102], or no intervention [103, 104], and one comparison between a transdermal patch and placebo [105].

Data from the four trials with a placebo or no intervention group did not suggest a causal association between COC or transdermal patch and weight change. Most comparisons of different combined hormonal methods showed no substantial difference in weight. The authors concluded that the current evidence was insufficient to clearly establish the effect of combination hormonal contraceptives on weight, but no large effect was evident.

DMPA and Weight Gain

Even more so than with combined hormonal contraceptives, there is a belief among clinicians and patients that DMPA use results in profound weight gain. A large body of literature attempts to assess weight gain in women using DMPA and the data are mixed, with some reports suggesting quite extensive weight gain and other reports showing no association.

A 2016 Cochrane review examined the evidence for weight change with progestin-only methods of contraception [106]. They reviewed 22 studies, of which 16 examined DMPA users. Overall, the quality of evidence was low as 17 of the 22 were nonrandomized studies.

In 15 of the studies, significant differences between progestin-only contraceptive users and comparison groups were not found when looking at weight change or body composition. When DMPA was compared to the copper IUD, three prospective studies showed no significant difference in weight change after adjustment for potential confounders. One retrospective study showed a mean weight difference for DMPA users compared to copper IUD users at 1, 2 and 3 years [107]. The mean weight gain ranged from 1.79 kg to 3.83 kg per year for DMPA, compared to 1 kg per year for the Copper IUD group. Notably, when BMI subgroups were analyzed, DMPA-associated weight gain was greater only for normal weight and overweight women, but not for obese groups.

Another study retrospectively compared weight change in users of DMPA, LNG IUS, and copper IUD over 10 years. Results suggested a statistically significant difference in weight gain between DMPA and the IUDs, with DMPA mean weight gain of 6.6 kg, LNG IUS of 4.0 kg, and copper IUD of 4.9 kg ($p = 0.0197$) [108]. However, conclusions should be interpreted with caution, as the study groups had

significant attrition by 10 years due to discontinuation of methods. Also, BMI, age, and level of education were significantly different between groups.

The review concluded that results of all the studies were mixed, but generally suggest minimal, if any, weight gain with studies reporting at most 2–4 kg/year. Most of the literature available to examine these questions is of low quality, given noncontrolled study design and high potential of bias due to contraceptive discontinuation and participant attrition.

Two newer studies provide additional information on DMPA and body weight changes, but still do not provide conclusive evidence for a causal relationship between DMPA and weight gain. The first trial examined weight and body mass in DMPA users compared with copper IUD users over a 12-month period. Body weight increased 1.9 kg ($p = 0.02$) in DMPA users at 12 months, resulting from an increase of 1.6 kg ($p = 0.03$) in fat mass. Weight was unchanged in IUD users, and an increase in lean mass at 12 months ($p = 0.001$) in this group was attributed to increased physical activity [109]. The second recent study compared weight gain in users of DMPA, the LNG-IUS, the etonogestrel implant, and the copper IUD. The mean weight gain in each of these groups was 2.1, 1.0, 2.2, and 0.2 kg, respectively, but the ranges in weight change were broad within each study group. Study findings suggest highly variable weight gain in all progestin-only contraceptive users [110].

One important area of potential concern regarding DMPA and weight gain is weight change in adolescents who are already obese at DMPA initiation. Studies suggest that overweight or obese adolescent DMPA users may gain more weight than normal-weight users. This association is not evident in adults [111].

Taken together, the current literature remains generally ambiguous about an association of DMPA with weight gain. Likely, weight gain secondary to DMPA use is modest, and it may not be remarkably different than usual changes in weight experienced by women over time, especially given the propensity to obesity in the United States and other regions of the developed world. This idea is supported by several studies using copper IUD control groups, which report annual weight gain not attributable to a hormonal contraceptive. Given the lack of data suggesting pathologic weight gain, DMPA should not be avoided based on fear of weight gain alone in most adult women.

Long-Acting Reversible Contraceptives and Weight Gain

Newer concerns regarding weight gain continue to emerge, for the progestin implants and IUDs, similarly to those for DMPA. Users' perception of weight gain with LARCs is reported as high as 34% [112].

Recent data reports statistically significant weight gain with the ENG implant, LNG implant, and LNG IUS, compared with the copper IUD. The magnitude of the weight is modest, ranging between 1 and 3 kg per year [110, 113]. Interestingly, changes in lean body mass over 12 months among users of ENG implant, LNG IUS, and the copper IUD were not significantly different [113]. Some data suggest more profound weight gain in older users, black women, and those with higher BMI at method initiation [110, 112, 113].

In the absence of data associating LARC and abnormal weight gain, clinicians should continue to recommend IUDs and implants as first-line options for many women. LARC methods are the most effect contraceptive methods and provide several non-contraceptive benefits.

Conclusions

When evaluating the controversies surrounding contraceptive care, the clinician must understand the emerging evidence in order to make appropriate clinical judgments and provide quality contraceptive care. Providers must counsel patients using current and accurate information, so that the patient can make an appropriate, informed choice about her best contraceptive options. Most women are good candidates for the indicated use of most birth control methods, but some women may have prevailing conditions that may preclude the use of hormonal or intrauterine contraception. The prescribing provider must take into account medical and social factors that impact successful contraceptive use, fertility control, and pregnancy planning, and address the risk of unintended pregnancy in each woman, regardless of which contraceptive methods may or may not be appropriate for use. An understanding of current evidence will thus permit the clinician to provide accurate and personalized counseling that will empower women to select a method that best suits their needs and thus prevent unintended pregnancy and its associated profound morbidity and mortality.

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