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Contraception Selection, Effectiveness, and Adverse Effects
A Review

Stephanie Teal, MD, MPH; Alison Edelman, MD, MPH

IMPORTANCE Many women spend a substantial proportion of their lives preventing or planning for pregnancy, and approximately 87% of US women use contraception during their lifetime.

OBSERVATIONS Contraceptive effectiveness is determined by a combination of drug or device efficacy, individual fecundability, coital frequency, and user adherence and continuation. In the US, oral contraceptive pills are the most commonly used reversible method of contraception and comprise 21.9% of all contraception in current use. Pregnancy rates of women using oral contraceptives are 4% to 7% per year. Use of long-acting methods, such as intrauterine devices and subdermal implants, has increased substantially, from 6% of all contraceptive users in 2008 to 17.8% in 2016; these methods have failure rates of less than 1% per year. Estrogen-containing methods, such as combined oral contraceptive pills, increase the risk of venous thrombosis from 2 to 10 venous thrombotic events per 10 000 women-years to 7 to 10 venous thrombotic events per 10 000 women-years, whereas progestin-only and nonhormonal methods, such as implants and condoms, are associated with rare serious risks. Hormonal contraceptives can improve medical conditions associated with hormonal changes related to the menstrual cycle, such as acne, endometriosis, and premenstrual dysphoric disorder. Optimal contraceptive selection requires patient and clinician discussion of the patient's tolerance for risk of pregnancy, menstrual bleeding changes, other risks, and personal values and preferences.

CONCLUSIONS AND RELEVANCE Oral contraceptive pills are the most commonly used reversible contraceptives, intrauterine devices and subdermal implants have the highest effectiveness, and progestin-only and nonhormonal methods have the lowest risks. Optimal contraceptive selection incorporates patient values and preferences.

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Author Affiliations: Department of OB/GYN, University Hospitals Medical Center and Case Western Reserve University, Cleveland, Ohio (Teal); Department of OB/GYN, Oregon Health & Science University, Portland (Edelman).

Corresponding Author: Stephanie Teal, MD, MPH, Department of OB/GYN, University Hospitals Medical Center and Case Western Reserve University, 11100 Euclid Ave, MAC-5304 Cleveland, OH 44106 (Stephanie.Teal@uhhospitals.org).

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Contraception is defined as an intervention that reduces the chance of pregnancy after sexual intercourse. According to a report from 2013, an estimated 99% of women who have ever had sexual intercourse used at least 1 contraceptive method in their lifetime.[1] Approximately 88% of sexually active women not seeking pregnancy report using contraception at any given time.[2] All nonbarrier contraceptive methods require a prescription or initiation by a clinician. Therefore, contraception is a common reason women 15 to 50 years of age seek health care.[3] This review summarizes current evidence regarding efficacy, adverse effects, and optimal selection of reversible contraceptives. This review uses the terms *women* and *men* when the biological expectation for the individual is ovulation or sperm production, respectively.

Methods

A search of OVID Medline All, Embase.com, and Ovid Evidence-Based Medicine Reviews–Cochrane Central Register of Controlled Trials for English-language studies was conducted for articles published between January 1, 2000, and June 28, 2021, to identify randomized clinical trials, systematic reviews, and practice guidelines related to contraception or contraceptives. After excluding duplicates and articles not relevant to this review, 2188 articles were identified as potentially relevant via title or abstract content. Thirty-seven articles, consisting of 13 randomized clinical trials, 22 systematic reviews, and 2 guidelines were included. Evidence-based guidelines that used GRADE and systematic reviews were selected for inclusion over individual studies. Clinical practice guidelines from the Society of Family Planning, the World Health Organization, and the American College of Obstetricians and Gynecologists on selected topic areas were reviewed to identify additional key evidence.

Results

The mean age of first sexual intercourse among females in the US is 17 years.[4] Many women typically use contraceptives for approximately 3 decades.[2] The choice of contraceptive is determined by patient preferences, tolerance for contraceptive failure, and adverse

Box. Commonly Asked Questions About Contraception

- **What options are available for male contraception?** There are currently no Food and Drug Administration–approved contraceptive options for men except condoms. Current male contraceptive methods under evaluation attempt to suppress sperm count to <1 million/mL and include a testosterone plus progestin topical gel.
- **Are contraceptives associated with increased rates of cancer?** Combined hormonal contraceptives, such as combined oral contraceptive pills, protect against endometrial and ovarian cancer. They are associated with an increased risk of early breast cancer diagnosis in current or recent users (ie, within the past 6 mo). The incidence is 68 cases per 100 000 person-years compared with 55 cases per 100 000 nonuser-years. There are no associations of past contraceptive use with increased rates of cancer and there is no association of past contraceptive use and mortality.
- **Can teenagers use intrauterine devices (IUDs)?** Prior guidance suggested restricted use of IUDs by teenagers, nonmonogamous or unmarried, and nulliparous women, but there is no high-quality evidence to support this recommendation. None of these characteristics are true contraindications.
- **Should all women use the most effective form of contraception?** The choice of contraceptive is determined by patient preferences and tolerance for failure. Patients may value other attributes of a method (such as route of administration or bleeding patterns) more highly than effectiveness, and may prefer to have a slightly higher risk of unplanned pregnancy to avoid other adverse effects.
- **Is the pill as effective for individuals with obesity?** Obesity adversely influences contraceptive steroid levels but determining whether this affects contraceptive effectiveness is difficult. The primary reason for contraceptive failure is suboptimal adherence. The use of any method for individuals no matter their weight will prevent more pregnancies than not using a method.
- **Why are pills not available over the counter (OTC)?** Combined hormonal contraceptives are unlikely to be available OTC in the US due to concerns regarding increased rates of thrombosis. Efforts to bring progestin-only pills OTC are progressing.

effects. Clinicians should elicit patient preferences, identify possible contraindications to specific contraceptives, and facilitate contraceptive initiation and continuation. Clinicians should also be prepared to address misperceptions (**Box**). Some experts recommend screening for contraceptive need at each visit. Two validated screening options, with toolkits available online, are One Key Question and the PATH questions (Pregnancy Attitudes, Timing, and How important is pregnancy prevention).[5,6]

Contraceptive Methods

Reversible contraceptive methods are typically grouped as hormonal (such as progestin-only pills or estrogen-progestin patches) or nonhormonal (condoms, diaphragms) and long-acting (such as intrauterine devices [IUDs]) or short-acting (such as pills). Reversible contraceptive methods can also be grouped by level of effectiveness for pregnancy prevention. Except for behavioral methods, condoms, and spermicide, contraceptive methods are only available by prescription in the US.

Hormonal Contraceptives

Pharmacology of Steroidal Hormone Components

Progestins and estrogens are steroid or lipid hormones. Hormonal contraception contains a progestin with or without an estrogen. Progesterone is the only naturally occurring progestin; most contraceptive progestins, such as levonorgestrel and norethindrone, are synthesized from testosterone. Progestins provide a contraceptive effect by suppressing gonadotropin-releasing hormone from the hypothalamus, which lowers luteinizing hormone from the pituitary, which in turn prevents ovulation.[7,8] In addition, progestins have direct negative effects on cervical mucus permeability. Progestins reduce endometrial receptivity and sperm survival and transport to the fallopian tube.[9-11] Estrogens enhance contraceptive effectiveness by suppressing gonadotropins and follicle-stimulating hormone, preventing the development of a dominant follicle. However, the most important contribution of estrogens to progestin-based contraceptives is the reduction of irregular bleeding. The estrogen component in most combined hormonal contraceptives is ethinylestradiol.

Progestin-Only Contraception

A variety of progestin-only contraceptive methods exists (**Table 1**). Their effectiveness varies based on dose, potency, and half-life of the progestin as well as user-dependent factors, such as adherence to the prescription schedule.[12,13]

Progestin-only pills include norethindrone- and drospirenone-containing formulations, which differ in their ability to suppress ovulation. Norethindrone pills contain 300 µg of norethindrone compared with 1000 µg in a typical combined contraceptive pill. The lower amount of progestin in norethindrone pills results in less consistent ovulation suppression and more potential for breakthrough bleeding. The contraceptive efficacy is maintained by other progestin-mediated effects. Drospirenone-only pills contain slightly more progestin than an estrogen and progestin combined hormonal contraception, which aids in ovulation suppression. In one study in which participants delayed their drospirenone-containing pill intake by 24 hours, mimicking a missed dose, ovulation suppression was maintained with only 1 participant of 127 having evidence of ovulation.[14] The benefits of progestin-only contraceptive pills include ease of initiation and discontinuation, fertility return within 1 cycle, safety profile, and minimal effect on hemostatic parameters.[15]

Depot medroxyprogesterone acetate (DMPA) is an injectable progestin available in intramuscular (150 mg) and subcutaneous (104 mg) formulations, which are administered at 12- to 14-week intervals. While DMPA is associated with irregular uterine bleeding, this pattern improves with longer duration of use. A systematic review of DMPA-related bleeding patterns (13 studies with 1610 patients using DMPA) found that 46% of those using DMPA were amenorrheic in the 90 days following the fourth dose.[16] DMPA is the only contraceptive method that can delay return to fertility. The contraceptive effect and cycle irregularity can persist for up to 12 months after the last dose,[17] likely due to persistence in adipose tissue and its effectiveness in suppressing the hypothalamic-pituitary-ovarian (HPO) axis. DMPA may be best suited for those who benefit from amenorrhea (eg, patients with developmental disabilities, bleeding diatheses) but not by those who want to conceive quickly after discontinuation. Typical effectiveness of DMPA and progestin-only contraceptive pills is 4 to 7 pregnancies per 100 women in a year.[12,18]

Table 1. Summary of Contraceptive Methods

Method category	Components	Types	Typical effectiveness	Eligibility	When to start	When does it start working for pregnancy prevention?	How to use	How to prescribe	Unique features
Combined hormonal contraceptive methods (CHCs)[a]	Estrogen + progestin	Oral pills, vaginal rings, transdermal patches	Moderately effective 4-7 Pregnancies per 100 women in a year	See MEC for CHCs Contraindications mostly related to those at risk for deep venous thrombosis such as age >35 y and current cigarette smoking or history of venous thrombosis	Any time, immediately	Effective immediately if started within the first 5 d of menses. If started at any other time, back-up method (eg, condom) should be used or abstinence for 7 d	Pill: take 1 pill daily Ring: place ring for 21 d, out for 7 d Patch: place 1 patch each wk for 3 wk, then off for 7 d Of note, some methods can be used continuously (no placebo week) or the withdrawal week can be shortened (see text)	13 Cycles, consider 1 refill	User controlled Short-acting: require daily, weekly, or monthly use Regular bleeding pattern
Progestin-only methods	Progestin	IUDs, subdermal implant, oral pills, injectable (subcutaneous and intramuscular)	IUDs and implant: highly effective, 1 pregnancy or less per 100 women in a year Pills and injectable: moderately effective, 6-10 pregnancies in 100 women in a year	See MEC for each progestin-only method[b]	Any time, immediately	Effective immediately if started within the first 5 d of menses. If started at any other time, back-up method (eg, condom) should be used or abstinence for 7 d	IUD: duration of use varies by IUD type (below) Implant: duration of use is 3-5 y Pill: take 1 pill daily Injectable: repeat injection every 13-15 wk. If >15 wk, review risk of pregnancy, if reasonably certain not pregnant (see Box), give next shot (FDA approved for 3; evidence-based duration, 5 y) Of note, all progestin-only methods are continuous (no placebo week) except the progestin-only pill containing drosperinone	IUD and implant: placed by provider Injectable: repeat injection every 13-15 wk Pills: 13 cycles, consider 1 refill	Safely used in those with medical comorbidities Lighter and less bleeding, may be unpredictable, or no bleeding at all

(continued)

Table 1. Summary of Contraceptive Methods (continued)

Method category	Components	Types	Typical effectiveness	Eligibility	When to start	When does it start working for pregnancy prevention?	How to use	How to prescribe	Unique features
Nonhormonal methods	Variable, nonhormonal Of note, some barrier methods contain latex	Copper IUD Barrier (condoms, diaphragm, agents that kill sperm or impair sperm motility) Behavioral (fertility awareness,[c] withdrawal)	IUD <1 pregnancy in 100 women-years Barrier: 13-21 pregnancies in 100 women-years Behavior: up to 22 pregnancies in 100 women-years Less-effective methods: ≥13 pregnancies per 100 women-years	IUD and barrier: few contraindications to use Fertility awareness[c]: individuals with regular cycles	IUD: any time, immediately Barrier: coital-dependent Fertility awareness[c]: after tracking for a few cycles	IUD: effective immediately Condoms: effective immediately Nonoxynol-9 spermicide: place at least 10-15 min prior to intercourse pH modulator gel: place immediately or up to 1 h before intercourse Fertility awareness[c]: after tracking a few cycles	IUD: duration of use varies on IUD type Condoms: place immediately prior to intercourse Diaphragm: add contraceptive gel and place <2 h prior to intercourse, afterwards leave in place for at least 6 h but no longer than 24 h Nonoxynol-9 spermicide: place at least 10-15 no more than 30-60 min before intercourse Reapply for subsequent intercourse pH modulator gel: place immediately prior or up to 1 h before intercourse Reapply for subsequent intercourse Fertility awareness[c]: requires training in recognition of physical signs and symptoms of preovulatory phase, effective communication, and periodic abstinence	IUD: placed by provider Condom: no prescription. Over the counter Diaphragm: prescription needed. Many pharmacies do not have in stock. Often easier to get online[b] Nonoxynol-9 spermicide: no prescription needed, over the counter pH modulator gel: prescription needed. Administer 1 applicator intravaginally immediately before or 1 h before intercourse (1 box contains 12 applicators)	Copper IUD can also be used for emergency contraception Condoms also provide STI protection Nonhormonal Some of these methods are available without a prescription

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; MEC, Medical Eligibility Criteria; IUDs, intrauterine devices; STI, sexually transmitted infection.

[a] CHCs are estrogen containing and thus are associated with an increased risk of venous thrombosis.

[b] Diaphragm: 3 types of silicone-based diaphragms are available: a 1-size fits most (Caya, which is distributed in the US by HPS RX Enterprises; https://www.hpsrx.com/) and 2 Milex diaphragms with differing rim styles in 8 different sizes (Arcing and Omniflex; Cooper Surgical; https://www.coopersurgical.com/detail/milex-arcing-style-diaphragm/ and https://www.coopersurgical.com/detail/milex-omniflex-style-diaphragm/).

[c] Fertility awareness indicates monitoring of physical changes, such as temperature rise and cervical mucus thickening, that indicate ovulation has occurred for that cycle.

Progestin-only long-acting methods, such as the levonorgestrel (LNG) IUD and the subdermal implant, have typical effectiveness rates of less than 1 pregnancy per 100 women per year similar to permanent methods, such as tubal ligation or vasectomy (**Table 2**).[12,18] These methods are also associated with return to fertility within 1 cycle after discontinuation. The LNG IUD maintains efficacy for at least 7 years, with amenorrhea rates of up to 20% at 12 months and 40% at 24 months.[19] However, initiation requires an in-person visit with a clinician trained in IUD placement. The etonogestrel subdermal implant is effective for up to 5 years[20] and is easily placed or removed. Initiation and discontinuation also require in-person visits. The bleeding profile of the implant is less predictable and up to 11% of users remove it in the first year due to irregular bleeding.[21] An analysis of 11 studies (923 participants) from Europe, Asia, South America, and the US found that the bleeding pattern in the first 3 months (such as prolonged, frequent, or irregular episodes) is consistent with future bleeding patterns.[21] However, those with frequent or prolonged bleeding in the first 3 months have a 50% chance of improvement in the subsequent 3 months.[21]

Combined Hormonal Contraception

Combined hormonal methods that contain both estrogen and progestin include the daily oral pill, monthly vaginal ring, and weekly transdermal patch. With full adherence, effectiveness of these methods is 2 pregnancies per 100 users per year. However, typical effectiveness is 4 to 7 pregnancies per 100 women per year, with variability in effectiveness related to the user's adherence.[12,18] The importance of patient adherence to hormonal contraception was recently demonstrated by a cohort study of approximately 10 000 individuals in the US. Pregnancy rates were 4.55 per 100 participant-years for short-acting methods (pills, patch, ring) compared with 0.27 for long-acting reversible methods (IUD, implant).[13] Women younger than 21 years using short-acting methods had higher pregnancy risk as women 21 or older (adjusted hazard ratio, 1.9 [95% CI, 1.2-2.8]).[13] No risk differences by age were observed for the long-acting reversible methods of IUD or implant. Absolute rates were not reported by age stratum.

Combined hormonal contraceptives prevent pregnancy through the same mechanisms as progestin-only methods. Their greatest advantage over progestin-only methods is their ability to produce a consistent, regular bleeding pattern. In a study that compared bleeding diaries from 5257 women using 9 different methods of contraception (nonhormonal, combined hormonal contraception, and progestin-only), approximately 90% of combined hormonal contraception pill users (n = 1003) over a 90-day standard reference period reported regular scheduled withdrawal bleeds while no one experienced amenorrhea.[22] Occasionally, patients do not have a withdrawal bleed during the placebo week. A pregnancy test can be performed if the patient or clinician is concerned about the possibility of pregnancy as the reason for not bleeding. If pregnancy is ruled out, the lack of withdrawal bleeding is due to HPO axis suppression and patients can be reassured that lack of withdrawal bleeding does not indicate a health problem or reduced fertility.

Considerations With Hormonal Contraception

Regardless of the route of delivery, ethinylestradiol and other estrogens are metabolized by the liver and activate the hemostatic system. The most significant risk of combined hormonal contraception is estrogen-mediated increases in venous thrombotic events.[23-25] Large international cohort studies have identified the risk of deep vein thrombosis at baseline in reproductive-aged women to be approximately 2 to 10 per 10 000 women-years. The risk associated with combined hormonal contraception is approximately 7 to 10 venous thrombotic events per 10 000 women-years.[26-28] The risk of venous thromboembolism is substantially greater in pregnancy. One UK study of 972 683 reproductive-aged women with 5 361 949 person-years of follow-up found a risk of deep vein thrombosis of 20 per 100 000 in women who were not pregnant. This rate increased to 114 per 100 000 women-years in the third trimester of pregnancy and to 421 per 100 000 in the first 3 weeks postpartum.[29] The absolute risk of ischemic stroke in reproductive-aged women not taking combined hormonal contraception is 5 per 100 000 women-years.[25] Combined hormonal contraception is associated with an additional absolute risk of approximately 2 per 100 000 (ie, overall risk of 7 per 100 000).[25] This study did not exclude women who smoked cigarettes or had hypertension.[25]

Clinicians who prescribe combined hormonal contraception should counsel women regarding signs and symptoms of arterial and venous thrombosis, especially for women with multiple additional risk factors, including body mass index (calculated as weight in kilograms divided by height in meters squared) at or over 30, smoking, and age older than 35 years. While progestins are not associated with an increase in thromboembolic risks,[30,31] US Food and Drug Administration package inserts for these methods contain "class labeling" or the same risks as estrogen and progestin combined hormonal contraceptive methods. Patients at increased risk of thrombosis can be provided a progestin-only, nonestrogen-containing method because this method of contraception does not increase risk of venous thromboembolism.[32]

Nonhormonal Contraceptives

Behavioral Methods

Behavioral contraceptive methods include penile withdrawal before ejaculation and fertility awareness–based methods. Imprecise terms, such as *natural family planning*, the *rhythm method*, or other euphemisms may be used by patients when referring to these methods. The effectiveness of withdrawal and fertility awareness depends on patient education, cycle regularity, patient commitment to daily evaluation of symptoms (first morning temperature, cervical mucus consistency), and the patient's ability to avoid intercourse or ejaculation during the time of peak fertility. Data on pregnancy rates are frequently of poor quality and highly dependent on study design.[33] A meta-analysis of higher-quality prospective studies of women at risk for undesired pregnancy reported failure rates of 22 pregnancies per 100 women-years for fertility awareness methods.[34]

Condoms and Diaphragms (Barrier Methods)

Other nonhormonal methods prevent sperm from entering the upper reproductive tract through a physical barrier (condoms and diaphragms) or through agents that kill sperm or impair their motility (spermicides and pH modulators). First-year typical use effectiveness for these methods is 13 pregnancies per 100 women in a year.[12,18]

Table 2. Summary of Currently Available Intrauterine Devices[a]

	Description	Current duration of approved use by FDA	Efficacy	Size of device	Other benefits	Bleeding pattern	Adverse effects
Copper T380A							
ParaGard	T-shaped polyethylene frame with approximately 176 mg of copper wire coiled along the vertical stem and a 68.7-mg collar on each side of the horizontal arm with white threads	10 y	>99%	32 mm × 36 mm	Can be used as emergency contraception Contains no hormones	First 3-6 mo: increased amount and duration of bleeding Common bleeding pattern: typically heavier and longer with approximately 50% increase in blood loss Proportion with no bleeding: 0%	Menstrual bleeding changes (heavier and longer periods); cramping after insertion and/or during periods
Hormonal IUDs							
Mirena	T-shaped polyethylene frame with a steroid reservoir containing 52 mg of LNG; releases approximately 20 µg per d, decreasing to 10 µg after 5 y. Silver threads	7 y for contraception 5 y for heavy menstrual bleeding	>99%	32 mm × 32 mm	May reduce period cramps and make menstrual period lighter FDA approved to treat heavy menstrual bleeding	First 3-6 mo: unpredictable with frequent light bleeding Common bleeding pattern: decreases menstrual bleeding with up to 90% reduction by 6 mo Proportion with no bleeding: 1 y: 20%, 5 y: 40%	Menstrual bleeding changes (spotting, lighter or absence of periods); cramping after insertion; abdominal or pelvic pain; benign ovarian cysts; headache or migraine; increased vaginal discharge, vulvovaginitis
Liletta	T-shaped polyethylene frame with a drug reservoir containing 52 mg of LNG, releases approximately 18.6 µg per d, decreasing to 12.6 µg per d at 3 y. Blue threads	6 y	>99%	32 mm × 32 mm	May reduce period cramps and make menstrual period lighter	First 3-6 mo: increased amount of bleeding and irregular spotting Common bleeding pattern: regular menstrual bleeding decreases, but irregular bleeding and spotting may continue Proportion with no bleeding: 1 y: 20%, 3 y: 40%	Menstrual bleeding changes (spotting and lighter periods); cramping after insertion or during periods; benign ovarian cysts; vaginal/vulvovaginal infection; acne
Kyleena	T-shaped polyethylene frame with steroid reservoir containing 19.5 mg of LNG, releases approximately 17.5 µg per d, decreasing to 7.4 µg per d after 5 y. Silver ring visualized on ultrasound and blue threads	5 y	>99%	28 mm × 30 mm	May reduce period cramps and make menstrual period lighter	First 3-6 mo: increased amount of bleeding and irregular spotting Common bleeding pattern: regular menstrual bleeding decreases, but irregular bleeding and spotting may continue Proportion with no bleeding: 1 y: 10%, 5 y: 20%	Menstrual bleeding changes (spotting and lighter periods); cramping after insertion or during periods; vulvovaginitis; benign ovarian cyst; acne abdominal/pelvic pain; headache/migraine
Skyla	T-shaped polyethylene frame with a steroid reservoir containing 13.5 mg of LNG; releases approximately 14 µg per d, decreasing to 5 µg per d after 3 y. Silver ring visualized on ultrasound and silver threads	3 y	>99%	28 mm × 30 mm	May reduce period cramps and make menstrual period lighter	First 3-6 mo: increased amount of bleeding and irregular spotting Common bleeding pattern: regular menstrual bleeding decreases, but irregular bleeding and spotting may continue Proportion with no bleeding: 1 y: 5%, 3 y: 10%	Menstrual bleeding changes (spotting and lighter periods); cramping after insertion or during periods; vulvovaginitis; benign ovarian cyst; abdominal/pelvic pain; headache/migraine; acne

Abbreviations: FDA, Food and Drug Administration; IUD, intrauterine device; LNG, levonorgestrel.

[a] Benefits of IUDs: long-term reversible birth control as effective as sterilization, no long-term fertility effects after stopping, can be used for those who cannot or prefer not to take estrogen, no age restrictions with use after menarche, nulliparous patients can use, and can be used while breastfeeding.

Copper-Bearing IUD

The copper-bearing IUD is a highly effective nonhormonal reversible method.[12,18] Typical use pregnancy rates are 1% per year.[12,18] There is no effect on a user's HPO axis and thus ovulation and menstrual cyclicity continues. The primary mechanism of action is spermicidal, through direct effects of copper salts and endometrial inflammatory changes.[35] The major challenge with the copper IUD is that it can increase the amount, duration, and discomfort of menses mostly during the first 3 to 6 months of use.[36] IUD use does not increase later risk of tubal infertility.[37] If sexually transmitted infection (STI) testing is indicated, testing can be performed concurrently with IUD placement.[38-40] This expedited process of testing for STIs at the time of IUD placement does not increase the risk of pelvic inflammatory disease. The absolute risk of pelvic inflammatory disease after IUD insertion is low in those with (0%-5%) or without (0%-2%) existing gonorrhea or chlamydial infection.[41]

Emergency Contraception

Emergency contraception (EC) reduces pregnancy risk when used after unprotected intercourse. The most effective method of EC is a copper IUD, which reduces pregnancy risk to 0.1% when placed within 5 days of unprotected intercourse.[42] A copper IUD also has the added advantage of providing patients with ongoing contraception. LNG IUDs were not previously considered an option for EC. However, in a recent randomized noninferiority trial, women requesting EC who had at least 1 episode of unprotected intercourse within the prior 5 days were randomized to receive a copper IUD (n = 356) or a 52-mg LNG IUD (n = 355).[43] LNG IUD was noninferior to copper IUD (between-group absolute difference, 0.3% [95% CI, −0.9% to 1.8%]). However, the proportion of study participants who had unprotected intercourse midcycle (and therefore were at risk of pregnancy) was not reported. If a patient needs EC and wishes to initiate a 52-mg LNG IUD, it is reasonable to immediately place the IUD plus give an oral EC,[44] given the limited and indirect evidence supporting the LNG IUD alone for EC.

Oral EC consists of a single dose of either a progestin (LNG, 1.5 mg) or an antiprogestin (ulipristal acetate, 30 mg). Both of these agents work by blocking or delaying ovulation. Neither is abortifacient. LNG EC is available over-the-counter; a prescription is needed for ulipristal acetate. The medication should be taken as soon as possible after unprotected intercourse for maximum efficacy but can be taken up to 5 days afterward for ulipristal acetate.[45-47] LNG efficacy is diminished after 3 days. Efficacy appears similar between the 2 agents when ingested within the first 72 hours after intercourse (ulipristal acetate EC: 15 pregnancies of 844, LNG EC: 22 pregnancies of 852; reduction in pregnancy without EC use estimated to be 90% less) but pharmacodynamic and clinical studies demonstrated that the ulipristal acetate treatment effect persists up to 120 hours with no pregnancies (0/97).[46] Actual use studies of EC that included 3893 individuals found lower pregnancy prevention rates than expected, which appears to be related to multiple acts of unprotected intercourse both before and after the EC use.[48,49] If further acts of unprotected intercourse occur 24 hours after EC use and a regular method of contraception has not been started, EC needs to be taken again.[49] Repeat use of LNG EC results in no serious adverse events; repeat dosing for ulipristal acetate EC has not been specifically studied.[50] Clinicians should review the options for EC with all patients starting a user-controlled method, such as condoms. These patients may be prescribed oral EC to keep at home for immediate use if needed.

Evidence-Based Clinical Tools to Aid in Prescribing

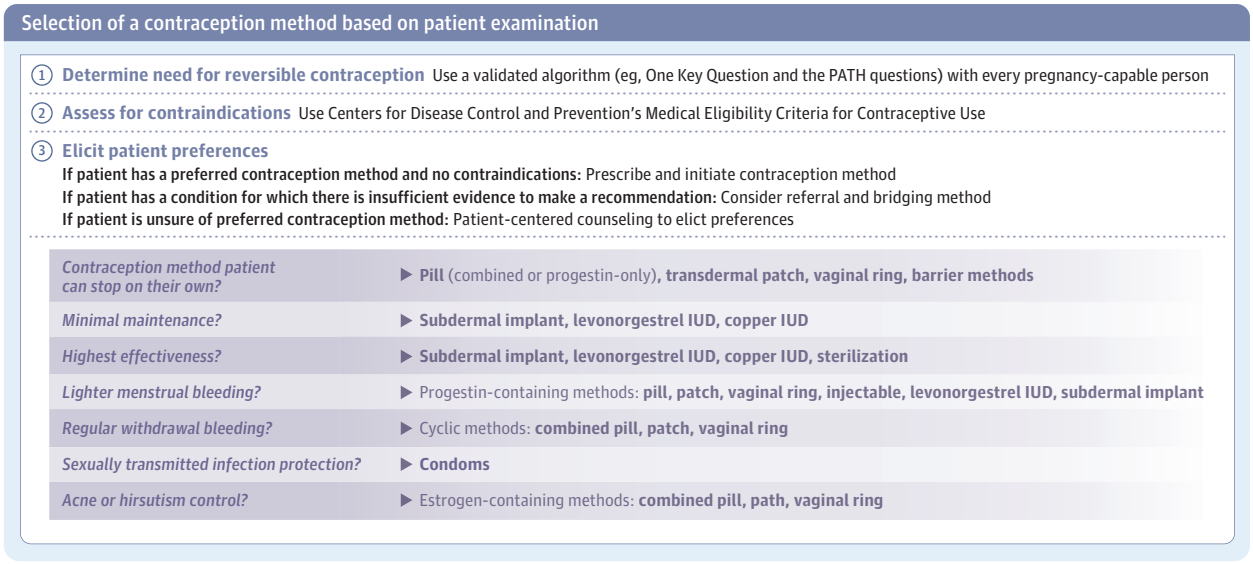
Two evidence-based guidelines are available to assist clinicians in evaluating the safety of contraception initiation and use.[32,42] These guidelines were developed by the US Centers for Disease Control and Prevention, are updated regularly, and are freely available online and in smartphone apps.

The first is the US Medical Eligibility Criteria for Contraceptive Use[32] (US MEC), which provides information on the safe use of contraceptive methods for women with various medical conditions (eg, diabetes, seizure disorder) and other characteristics (eg, elevated body mass index, tobacco use disorder, postpartum). The US MEC uses a 4-tiered system to categorize level of risk for each disease/contraceptive method combination.[32] The risk tiers are (1) no restrictions exist for use of the contraceptive, (2) advantages generally outweigh theoretical or proven risks although careful follow-up might be required, (3) theoretical or proven risks outweigh advantages of the method and the method usually is not recommended unless other more appropriate methods are not available or acceptable, and (4) the condition represents an unacceptable health risk if the method is used.[32]

All clinicians, including advanced practice clinicians, should be familiar with prescribing within US MEC categories 1 and 2 (no restrictions or benefits outweigh risks). For women with underlying health conditions who want to use a category 3 method, such as a woman with a history of breast cancer choosing combined hormonal contraceptives, primary care physicians or specialists should review the detailed evidence listed in the US MEC to advise their patients. Subspecialists in complex family planning who have completed extra fellowship training may provide helpful consultation for patients with multiple contraindications or unusual situations. The US MEC is a guideline, not a mandate. Situations may arise in which specialists recommend an MEC category 3 or 4 method because the alternative to the contraceptive method, pregnancy, places the patient at even greater risk.[32] The US MEC does not include conditions for which there is insufficient evidence to make recommendations, such as aortic aneurysms, Marfan syndrome, or chronic marijuana use. For these patients, clinicians should consider referral to a complex family planning specialist. If the patient needs a method immediately, a progestin-only pill should be considered as a "bridging" method, because these can be used safely by most patients[32] and are more effective than barrier methods such as condoms.

The US MEC addresses common drug interactions with hormonal contraceptives.[32] Contraceptive steroid hormones are metabolized via the hepatic cytochrome P450 pathway.[51,52] Drugs that induce this pathway, such as rifampin and barbiturates, or chronic alcohol can impair contraceptive efficacy and drugs that inhibit the pathway, such as valproic acid, cimetidine, or fluconazole, may increase adverse effects. The FDA recognizes a drug-drug interaction as clinically significant if it causes at least a 20% difference in drug levels[53] but an interaction does not necessarily affect contraceptive failure rates. Adherence, continuation, fecundity, and frequency of intercourse also contribute to contraceptive effectiveness. Additionally, most pharmacokinetic studies do not have sufficient statistical power to determine differences in pregnancy

Figure 1. How to Choose a Contraceptive Method



This algorithm has not been validated for clinical use. IUD indicates intrauterine device; PATH, Pregnancy Attitudes, Timing, and How important is pregnancy prevention.

rates. The most common drug classes that may interact with hormonal contraceptives are antiretroviral drugs (including efavirenz and ritonavir-boosted protease inhibitors) and anticonvulsant therapies (including carbamazepine, phenytoin, and others).[54,55] Evidence from both clinical and pharmacokinetic studies of routinely used antibiotics do not support impaired contraceptive efficacy with concomitant antibiotic prescription,[56] except for rifampin with which ethinylestradiol and progestin area under the curve levels are at least 40% lower.[57] Because the local progestin dose in the LNG IUD is so high, its efficacy is not reduced by drugs that may affect combined hormonal contraceptives, progestin-only contraceptive pills, or the progestin implant. While hormonal contraceptive use can change concentrations of some drugs,[58] this is rarely clinically relevant, except for the reduction in serum concentration of the anticonvulsant lamotrigine.

Another major guideline is the US Selected Practice Recommendations for Contraceptive Use[42] (US SPR, available online or via a smartphone app). The US SPR is organized by contraceptive method. It includes method-specific, up-to-date guidelines, such as how to initiate the method, how to manage bleeding irregularities, and recommended follow-up. For example, the guidelines on IUDs include evidence on medications to ease IUD insertion or IUD management if a pelvic infection occurs. Recommendations related to combined hormonal contraceptives include the number of pill packs that should be provided at initial and return visits or management of vomiting or severe diarrhea while using combined oral contraceptives.

Noncontraceptive Health Effects of Hormonal Contraception

Much of the data on noncontraceptive benefits of hormonal methods come from case-control studies or small comparative trials. However, fair evidence exists that methods that suppress ovulation can be effective in reducing benign ovarian tumors[59] and functional ovarian cysts.[60] Combined hormonal contraceptives diminish hormonally mediated premenstrual dysphoric disorder, with statistically significant mean differences in symptoms, such as headaches, bloating, and fatigue, and functionality scales.[61] The estrogen component of combined hormonal contraception increases hepatic sex hormone–binding globulin, which reduces free testosterone and improves androgen-sensitive conditions, such as acne and hirsutism. Cochrane systematic reviews of combined hormonal contraceptives and both conditions show significant associations with improvement in a variety of measures of acne and hirsutism.[62,63] All progestin-containing contraceptives cause endometrial atrophy and, thus, reduce menstrual blood loss and menstrual pain to varying extents.[64-66] While progestin-only methods can promote unscheduled or breakthrough bleeding, the total amount of blood loss is reduced and in those with heavy menstrual bleeding, hemoglobin levels can rise by 10 g/L in 12 months.[67,68] The LNG IUD has demonstrated efficacy in reduction of heavy menstrual bleeding[69,70] (including for women with anticoagulation, fibroids,[71] or hemostatic disorders), primary dysmenorrhea,[36,72] endometriosis,[73] adenomyosis,[74] and protection against pelvic infection.[75]

Discussion

Initiating a Method of Contraception

Screening for pregnancy is important prior to prescribing contraception. According to the US SPR, clinicians should be "reasonably certain" that the patient is not pregnant.[42] A clinician can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any 1 of the following criteria: (1) is 7 days or less after the start of normal menses; (2) has not had sexual intercourse since the start of last normal menses; (3) has been correctly and consistently using a reliable method of contraception; (4) is 7 days

or less after spontaneous or induced abortion; (5) is within 4 weeks' postpartum; and (5) is fully or nearly fully breastfeeding (exclusively breastfeeding or most [≥85%] of feeds are breastfeeds), amenorrheic, and less than 6 months postpartum.

These criteria have a negative predictive value of 99% to 100%.[76-78] A urine pregnancy test (UPT) alone is not sufficient to exclude pregnancy. UPT sensitivity is dependent on when the last act of intercourse occurred, the ovulatory cycle phase, and urine concentration. Sensitivity of UPTs is 90% at the time of a missed period, but only 40% in the week prior.[79] Additionally, a UPT can remain positive up to 4 weeks after delivery, miscarriage, or abortion.[80,81] Few other tests are required for safe and effective use of contraception.

Clinicians can offer other indicated preventive health tests at the contraceptive initiation visit, like screening for cervical cancer or STIs. However, these tests are not required for contraceptive use and should not prevent initiation of contraception.

Generally, all methods should be started immediately on prescription regardless of menstrual cycle day—known as the Quick Start protocol.[82] If a hormonal method is initiated within 5 days of the first day of menses, no additional backup method is needed. At other times in the cycle, or when switching from a nonhormonal to a hormonal method, a backup is necessary for 7 days to ensure ovulation suppression. If switching from one hormonal method to another, the switch can occur without a withdrawal bleed or backup.

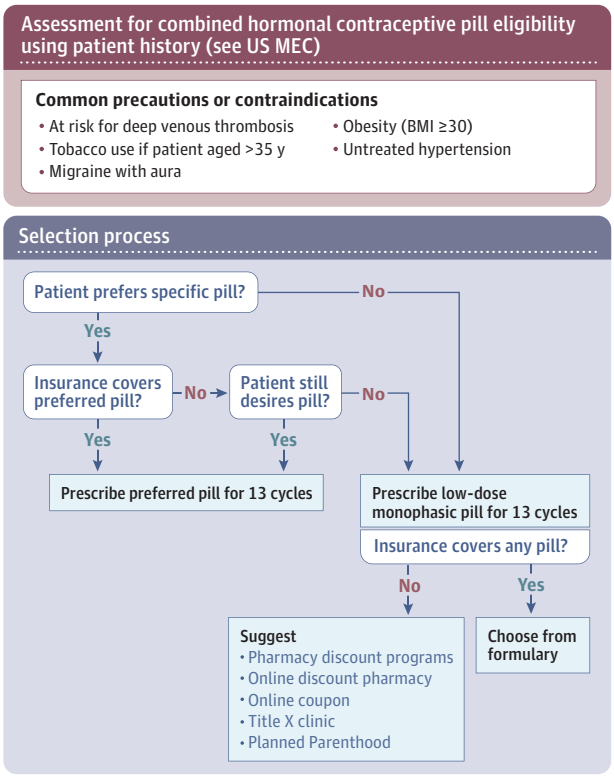
If a woman reports unprotected intercourse within the 5 days before contraceptive initiation, most sources recommend giving emergency contraception, initiating her desired method, and repeating a UPT 2 to 3 weeks later.[82-85] Many studies have demonstrated that exposing an early pregnancy to hormonal contraception is not harmful[86] but delayed initiation increases the risk of undesired pregnancy.

Selecting a Contraceptive Pill

Because comparative effectiveness studies to clearly identify the superiority of one contraceptive pill formulation over another are lacking, selecting a contraceptive pill often depends on patient experience. Monophasic regimens, in which each pill has the same hormone doses, have significant advantages over bi- and triphasic regimens. Cycles can be extended easily by skipping the placebo week and starting the next pack of active pills. If this is attempted with multiphasic regimens, the drop in progestin between phases typically results in breakthrough bleeding. In terms of ethinylestradiol, few patients require a pill containing more than 35 µg/d to prevent breakthrough bleeding.[87] Many clinicians advocate starting with the lowest ethinylestradiol dose to minimize risks. However, there are no data demonstrating that 10- to 20-µg/d ethinylestradiol doses are safer than 35 µg daily, and lower ethinylestradiol doses are associated with more unscheduled vaginal bleeding.[88] Thus, starting with a monophasic preparation containing 30 µg to 35 µg of ethinylestradiol provides the greatest likelihood of a regular bleeding pattern without increasing risk. Ethinylestradiol can be reduced if patients have estrogen-associated adverse effects, such as nausea or breast tenderness.

Many different progestins exist. Progestins differ in in vitro androgenicity, effects on surrogate metabolic markers, or similarity to testosterone.[89] While molecular structures differ, there is no evidence demonstrating that a particular progestin is superior to others. Traditionally, progestins were classified into "generations" by their parent compound and decade of development. This classification is not clinically useful and should be abandoned.[90] Patients sometimes prefer a pill that they used previously, and if no contraindications exist and the cost is acceptable to the patient, it is reasonable to prescribe it (**Figure 1** and **Figure 2**).

Figure 2. How to Prescribe a Combined Hormonal Contraceptive Pill



This algorithm has not been validated for clinical use. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); MEC, Medical Eligibility Criteria for Contraceptive Use.

Cyclic vs Continuous Dosing of Combined Hormonal Contraceptives

Combined hormonal contraceptives can be dosed in a cyclic or continuous fashion. Originally, birth control pills were dosed with 21 days of active drug and a 7-day placebo week to trigger a monthly withdrawal bleed, meant to mimic the natural menstrual cycle. However, many women prefer less frequent withdrawal bleeds.[91] Some women report significant adverse effects[92] during this placebo week, such as migraine, bloating, and pelvic pain, and extended use provides an easy way to manage or eliminate these problems.[61] During the placebo week, there is less suppression of the HPO axis.[93-95] For these reasons, many newer contraceptive pills have shorter (eg, 4-day) placebo periods. Further, most monophasic combined hormonal contraceptives can be used as extended use (fewer withdrawal bleeds) by having a 4-day placebo period quarterly or continuously (no withdrawal bleed) by eliminating the placebo altogether. Extended and continuous use are associated with improved typical use efficacy, likely because greater overall HPO axis suppression is achieved, which may offset lapses in user

adherence.[96] A new vaginal ring (segesterone acetate/ethinyl estradiol vaginal system) is also available, which is prescribed for 1 year, with the patient removing the ring each month for 7 days.[97]

Limitations

This review has several limitations. First, relatively few randomized clinical trials that directly compared contraceptive methods were available. Therefore, contraceptive methods are typically evaluated by their individual efficacy (pregnancies per person-cycles) and not typically by their relative effectiveness compared with another method. Second, the quality of summarized evidence was not evaluated. Third, some aspects of contraception, such as counseling, noncontraceptive health benefits, ongoing contraceptive innovations, and the effect of cultural values, and patient preferences were not covered in this review.

Conclusions

Oral contraceptive pills are the most commonly used reversible contraceptives, IUDs and subdermal implants have the highest effectiveness, and progestin-only and nonhormonal methods have the lowest risks. Optimal contraceptive selection incorporates patient values and preferences.

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