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Review

Contraceptive Selection for the Endocrine Patient: What an Endocrinologist Should Know

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Abstract

Although endocrinologists specialize in the management of hormones, they often lack sufficient training in the appropriate use of the diverse array of available contraceptive options. All medical providers should possess a fundamental understanding of contraceptive methods for pregnancy prevention, but endocrinologists should have a deeper understanding of birth control possibilities due to the useful role of hormone-containing contraception in managing endocrine and metabolic disorders. This manuscript outlines the history of contraception and then evaluates both existing and emerging birth control options for women and men. Delving further, this review also explores the impact of individual sex steroids—estrogens, progestins, and androgens—used in hormonal contraceptive methods. In addition to their role as contraceptives, the influence of these exogenous hormones on the hypothalamic-pituitary-gonadal axis warrants careful consideration. These effects extend beyond pregnancy prevention and can be instrumental in regularizing menses, sex steroid replacement, and androgen suppression. Finally, this review provides tailored suggestions for contraceptive usage in patients with endocrine disorders, ensuring comprehensive care and informed decision-making in clinical practice.

Key Words: combined hormonal contraception, sex steroids, hyperandrogenism, non-hormonal contraception, medical history

Abbreviations: AUC, area under the curve; BMI, body mass index; CAH, congenital adrenal hyperplasia; CHC, combined hormonal contraceptive; COCP, combined oral contraceptive pill; Cu, copper; DMPA, depot medroxyprogesterone acetate; E2, 17β-estradiol; E2V, estradiol valerate; E4, estetrol; EC, emergency contraception; EE, ethinyl estradiol; FAM, fertility awareness method; FDA, Food and Drug Administration; GAHT, gender-affirming hormone therapy; HPG, hypothalamic-pituitary-gonadal; IUD, intrauterine device; LARC, long-acting reversible contraceptive; NFP, natural family planning; P4, progesterone; PCOS, polycystic ovary syndrome; POP, progestin-only pill; STI, sexually transmitted infection; VTE, venous thrombotic event.

Essential Points

- While all medical providers should be familiar with the wide array of contraceptive methods available for pregnancy prevention, endocrinologists should have a more comprehensive understanding of the various birth control options—particularly hormone-containing contraception—due to their significant role in the management of endocrine and metabolic disorders.
- The backbone of all hormonal contraception currently available to females is a synthetic progestin, which, when delivered systemically in supraphysiologic doses, provides negative feedback on the hypothalamic-pituitary-gonadal axis, and subsequently inhibits ovulation, suppresses the endometrial lining, and prevents implantation.
- Synthetic estrogens can potentiate the effects of the progestin and offer additional benefits such as stabilizing bleeding patterns and increasing sex hormone binding globulin levels but carry increased risk of thromboembolic complications (eg, deep venous thrombosis, stroke).
- Progestins can act on different steroid receptors within the body and yield diverse clinical outcomes that can be leveraged to achieve the broader goals of patients with endocrine disorders, which extend beyond pregnancy prevention and encompass aspects such as sex steroid replacement, menstrual cycle regulation, or androgen suppression.
- There are several emerging hormonal and nonhormonal contraceptive methods that have been recently approved or are in the pipeline that endocrinologists may be able to use in the future, but for now offer exciting prospects for individuals or couples seeking alternative contraceptive options.

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History of Contraception

Contraception, defined as the intentional prevention of conception or impregnation, encompasses a range of artificial or natural methods, including drugs, devices, behaviors, or surgical procedures. As of 2018, approximately 1.9 billion women in the world were of reproductive age (15-49 years old) with 73 million women of these women living in the United States (1, 2). Females are typically fertile for 30 to 39 years, while the male reproductive age span is dependent on sperm count and quality, resulting in variability that extends well into the later decades of life (3-6). Throughout early human history, pregnancy was largely prevented through vaginal poultices made of natural materials or sea sponges soaked in various mixtures of naturally occurring substances that were then tied to a string to form a tampon-like plug (7). For example, the Ancient Egyptians used honey, acacia leaves, or lint to block sperm, whereas the silphium plant was used to great success by the Ancient Greeks to the point of extinction (8). Barrier methods—namely the male condom in the form of a linen sheath tied with a ribbon—were first used as early as 1000 BCE to prevent venereal disease. Though male condoms made from animal intestines gained recognition as a contraceptive option in the 16th century, it was not until the 1850s that condoms could be mass-produced in factories using vulcanized rubber (9). Similarly, descriptions of a primitive cervical cap made from half of a lemon was described by Casanova in the 1700s with the invention of the modern cervical cap occurring in the mid-1800s (8, 10).

The 19th century marked the first vasectomy in 1823, performed by British surgeon Sir Astley Paston Cooper, albeit on a dog. Vasectomies were performed in humans for nonsterilization reasons by the 1900s but were finally regarded as a contraceptive option during World War II (11). Concurrently, female sterilization in the form of suture ligation of the fallopian tubes was offered as a "permanent" contraceptive solution during cesarean sections or immediately postpartum by the 1880s. While other female surgical sterilization options have come and gone, tubal ligation stands out as a persistently popular permanent contraceptive method, gaining widespread acceptance as an option outside of pregnancy by the 1970s after advancements in fiberoptic and laparoscopic technology (12, 13). Bilateral salpingectomy, a form of female permanent contraception, replaced earlier forms of tubal ligation due to its safety, cost, and potential to prevent some forms of ovarian cancer (14).

Despite the evolution of nonhormonal contraceptive methods throughout the 1800s, the shifting social and political landscape in the Western world led activists such as Margaret Sanger to invest in additional effective contraceptive methods. However, it was Oscar Hertwig's groundbreaking work in sea urchins in 1875—proving that fertilization involved the union of an ovum with sperm—that ultimately led to a better understanding of fertility and the development of newer contraceptive options (15, 16). The "rhythm method," developed by Dr. Leo Latz in 1932, was designed around a better understanding of ovulation and the fertility window as described by Drs. Kyusaku Ogino and Hermann Knaus in the 1920s (17, 18). Sanger had been following these scientific developments and had long been interested in finding a "100% effective" contraceptive method for women. Although Sanger's motives for promoting birth control may be controversial, it is undeniable that her fervor for this topic was a major impetus in bringing an effective, hormonal birth control option to the market (19). With the financial backing of Katharine McCormick, Sanger was able to provide support to researchers Gregory Pincus and Min Chueh Chang in developing an oral contraceptive pill. This pill combined a synthetic progestin extracted from the Mexican wild yam with an estrogen to prevent pregnancy (20, 21). After successful clinical trials led by Dr. John Rock and backed by McCormick, the first oral contraceptive pill consisting of norethynodrel 9.85 mg/mestranol 0.15 mg (Enovid) received Food and Drug Administration (FDA) approval and entered the US market in 1960 (22).

As development of the first birth control pill advanced, research into contraceptive methods involving foreign objects inserted subdermally or into the uterine cavity also progressed. The earliest intrauterine device (IUD) emerged in the early 1900s and was made from silkworm intestine but was later replaced by ones made from polyethylene (ie, Lippes Loop) or stainless steel (ie, Dalkon shield) (23). Despite original enthusiasm for these hormonally inert devices, they were eventually removed from the market in the early 1970s due to patient discomfort as well as associations of the Dalkon shield with poor pregnancy outcomes, increased rates of pelvic inflammatory disease, sepsis, and even death largely attributed to the braided string of the Dalkon shield (12). The fallout from the Dalkon shield destroyed trust in contraceptive devices and nearly upended the use of IUDs in the United States, though interest in the IUD was revived in the late 1990s to early 2000s when newer forms—utilizing a monofilament IUD string—proved to have decreased side effects, fewer complications, and better long-term outcomes (24, 25).

The development of these newer IUDs and subdermal contraceptives took place in the 1960s—long before the Lippes Loop or the Dalkon Shield were discontinued. For example, the first International Conference on Intrauterine Contraception convened in 1962 and subsequent meetings led to the FDA approval of the first Copper IUD (Cu-IUD: TCu 200) in 1976 (26). On the heels of the Cu-IUD came the approval of the first contraceptive implant in the United States in 1990: subdermal levonorgestrel (Norplant). By 2002, the Norplant was removed from US markets due to unsubstantiated claims and lawsuits regarding coerced use in low-income women, complex removal procedures, and possible ineffectiveness due to low hormone release rates. The Norplant was quickly replaced by the etonogestrel implant (Implanon) in 2006 (27).

Advancements in our understanding of sex steroids and their effects on the reproductive cycle, coupled with developments in compounding materials for IUDs and implants, allowed for controlled drug release over longer periods. This led to an explosion of birth control options and ushered in the modern era of contraception. For example, the levonorgestrel IUD originated in Finland but the initial hormone-eluting IUDs were large, difficult to insert, and painful. With concern for potential risk of depression and breast cancer, modern levonorgestrel-containing IUDs have lower progestin doses, which have allowed for smaller profile hormonal IUDs, better patient acceptance, and fewer side effects (28-32).

At the same time, synthetic sex steroids were used for emergency contraception (EC). Initially, the Yuzpe method consisted of using any combined oral contraceptive pill in high

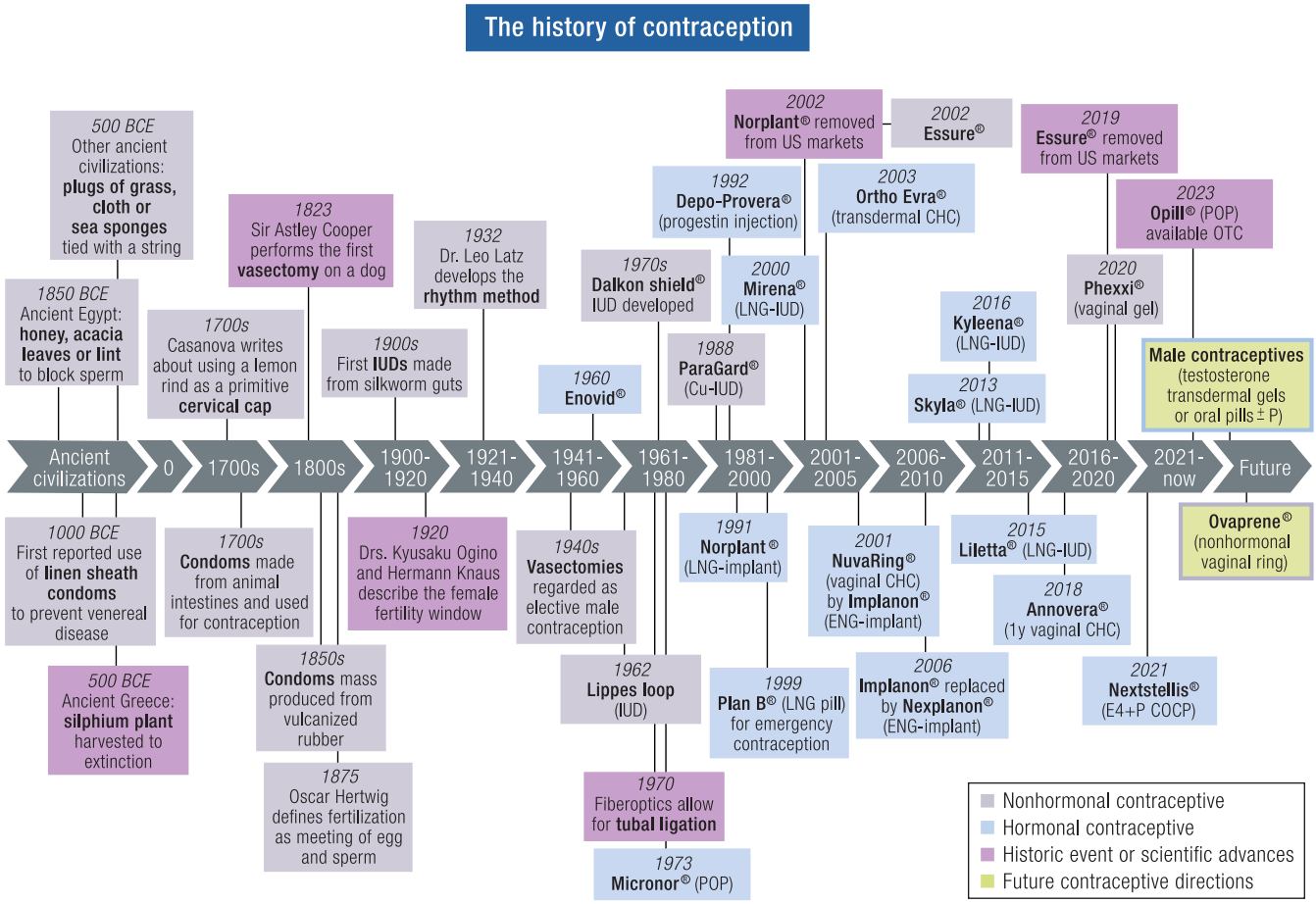

Figure 1. Timeline of various nonhormonal and hormonal contraception options alongside select historic events or scientific advances. Formulations of contraceptives (in alphabetical order): Annovera (segesterone acetate 0.15 mg/ethinyl estradiol 0.013 mg); Depo-Provera (medroxyprogesterone acetate 150 mg); Enovid (mestranol 0.15 mg/norethynodrel 9.85 mg); Implanon (etonogestrel 68 mg); Kyleena (levonorgestrel 19.5 mg); Liletta (levonorgestrel 52 mg);| Micronor (norethindrone 0.35 mg); Mirena (levonorgestrel 52 mg); Nexplanon (etonogestrel 68 mg radiopaque); Nextstellis (drospirenone 3 mg/estetrol 14.2 mg); Norplant (levonorgestrel 216 mg); NuvaRing (etonogestrel 0.120 mg/ethinyl estradiol 0.015 mg); Opill (norgestrel 0.075 mg); Ortho Evra (norelgestromin 0.15 mg/ethinyl estradiol 0.035 mg); Ovaprene (ferrous gluconate, ascorbic acid, glycine); ParaGard (T 380A intrauterine Copper device); Phexxi (lactic acid 1.8%, citric acid 1%, potassium bitartrate 0.4%); Plan B (levonorgestrel 1.5 mg); Skyla (levonorgestrel 13.5 mg).

Abbreviations: CHC, combined hormonal contraceptive; COCP, combined oral contraceptive pill; Cu, copper; E4, estetrol; ENG, etonogestrel; IUD, intrauterine device; LNG, levonorgestrel; P, progestin; POP, progestin-only pill.

doses for EC. Because of the high rates of nausea and vomiting with the Yuzpe method, oral levonorgestrel (Plan B) was developed specifically for EC and became available in 1999. EC was expanded to include the ulipristal acetate pill and the Cu-IUD (33, 34). This was quickly followed by FDA approval for the levonorgestrel IUD (Mirena) in 2001 to be used as a typical, non-EC option (28). By 2004, combined hormonal contraceptives in the form of the transdermal patch or the vaginal ring, as well as a progestin-only injectable, were in the contraceptive armamentarium available to women (Fig. 1) (35).

Modern contraceptive techniques derive from a foundation in an intimate understanding of reproductive biology. These methods strategically exploit the reproductive cycle, utilizing various sex hormone-responsive pathways to prevent the union of sperm and ovum or prevent implantation. The impact of hormonal contraception on the hypothalamic-pituitary-gonadal (HPG) axis and endometrium extends their applicability beyond pregnancy prevention, such as regularization of menses, sex steroid replacement, and/or androgen suppression. Such management frequently falls under the purview of endocrinologists, who must grasp the underlying mechanisms and appropriate use of these contraceptive methods for specific desired outcomes in the endocrine patient. While female contraceptive options abound, male contraception historically has relied on condoms and vasectomy for more than a century. Ongoing research into new male contraceptive methods holds promise for innovative options entering mainstream use in the future. In this review, we will delve into the wide array of hormonal and nonhormonal female contraceptive methods, as well as current and future male contraceptive options.

Contraceptive Options: Mechanisms of Action and Criteria for Effectiveness

Contraceptives can be broadly organized into nonhormonal or hormonal methods based on their mechanisms of action. However, birth control options can be further classified by their effectiveness in preventing pregnancy, potential for reversibility, or if the intended user is female or male (36, 37). There are at least 19 types of contraceptive options available, though several more are under development (7). Additionally, various surgical procedures (eg, endometrial ablation, uterine

artery embolization) may impact fertility potential but are not regarded as contraception given the need for continued use of effective contraception to prevent pregnancy among patients who have undergone these procedures (38). Even more definitive surgeries that completely impair fertility (eg, hysterectomy, bilateral ovariectomy) are not considered contraceptive options given their increased morbidity and mortality and thus are typically only indicated for the treatment of other medical conditions (eg, gynecological cancer, fibroids). These factors should be taken into consideration when making a contraceptive selection for the endocrine patient depending on the ultimate therapeutic goals.

The effectiveness of each contraceptive method in preventing pregnancy has been rigorously evaluated before approval by the FDA or other global regulatory agencies. Reported effectiveness is contingent upon optimal adherence (ie, perfect use), though it is also important to consider real life efficacy data (ie, typical use). Other factors, such as individual fecundability, partner cooperation in the method, coital frequency, compliance rates, and discontinuation rates, should also be taken into account (37, 39). Each patient and couple may also weigh the importance of relative effectiveness of a particular contraceptive method differently across the reproductive lifespan based on availability, cost, and cultural norms.

Nonhormonal Contraceptives

Nonhormonal contraceptive methods interfere with the reproductive process and hinder the union of egg and sperm by modifying physical aspects of the individual, such as anatomical structures or behaviors associated with fertility. While these options do not manipulate the sex-steroid profile, patients with endocrine concerns may still turn to nonhormonal contraceptives to prevent pregnancy or protect against sexually transmitted infections. As such, the various nonhormonal contraceptive options are briefly reviewed here.

Behavioral methods

All behavioral methods require that a couple adjusts their sexual behavior in some way and can be broadly categorized based on whether they are influenced by the menstrual cycle (40). Success in preventing pregnancy when utilizing behavioral methods additionally depends heavily on factors such as patient education, menstrual cycle regularity, and patient/partner commitment to avoiding intercourse during the fertile period (39). In a meta-analysis assessing contraceptive effectiveness, more than 37 randomized clinical trials, systematic reviews, and practice guidelines on contraceptive methods found that the combined pregnancy rate for behavioral types of contraception was 22 pregnancies/100 women per year (37). This failure rate may be deemed acceptable by some patients depending on their goals and values; however, it is significantly less effective than other contraceptive methods.

When classifying behavioral methods based on their dependence on the menstrual cycle, abstinence and coitus interruptus (also known as the withdrawal method) are the 2 behavioral methods that are independent of the menstrual cycle. Couples practicing abstinence refrain from any penile-insertive vaginal intercourse; thus, abstinence is 100% effective as contraception when used perfectly, but this rarely occurs in real life. In contrast, the withdrawal method entails removal of the penis from the vagina before ejaculation to prevent sperm from entering the female upper reproductive tract (40). However, it is known that the preejaculate secretions from the penis can contain viable sperm. This preejaculatory sperm in combination with potential male difficulty in ensuring appropriate withdrawal of the penis in a timely fashion before ejaculation result in lower rates of effectiveness among real world patients (41).

The fertility awareness method (FAM) and natural family planning (NFP) are the 2 behavioral contraceptive options that rely on the menstrual cycle and therefore their use should be limited to women with normal menses (cycle length between 21 and 35 days; average, 28 days). Furthermore, a proficient grasp of reproductive physiology is essential for couples engaging in FAM or NFP, as it helps mitigate the risk of fertilization on the female partner's fertile days. Studies indicate a higher incidence of unplanned pregnancies among individuals or couples lacking this crucial understanding, though 1 longitudinal study demonstrated high effectiveness (0.43% unintended pregnancies per year) when couples used these methods correctly (42-44). FAM relies on females to monitor physiologic changes (eg, cervical mucus changes, basal body temperature) suggestive of entering the fertile window (ie, impending ovulation or post-LH surge, respectively) during the menstrual cycle, whereas couples practicing NFP use a menstrual calendar to distinguish between fertile from nonfertile days (45, 46). In the modern era, several mobile applications and wearable devices exist to help couples track fertility, yet few are accurate or FDA-approved for this purpose (47-49). FAM and NFP are commonly used together, and may be used in conjunction with abstinence, withdrawal, or barrier methods during sexual intercourse on fertile days.

Barrier or mechanical methods

Barrier contraceptives are designed to impede sperm from entering the female upper reproductive tract. Among these, synthetic latex condoms remain the most widely used barrier method globally and represent 1 of 2 primary contraceptive options available for males (7). Other types of nonlatex condoms available include those made from polyisoprene, polyurethane, and lambskin. Condoms also serve as first-line methods for prevention of sexually transmitted infections (STIs) and both latex and nonlatex condoms provide reliable protection, except for lambskin condoms that contain pores large enough to allow for sexually transmitted infection transmission though still small enough to prevent sperm transport. For females, 3 barrier methods are available: the female latex or nitrile condom, diaphragms, and cervical caps (50). Contemporary diaphragms and cervical caps are constructed using silicone and must be used with spermicides to achieve contraceptive efficacy. While the overall efficacy of silicone-based female barrier methods is comparable to their rubber predecessors, the side effect profile may be more favorable for silicone compared to latex (50). The role of spermicides is to either kill sperm or impair sperm motility. They are available in various forms such as foam, jelly, cream, or sponge, with compositions including detergents (typically nonoxynol-9) that disrupt the sperm cell membrane, or acid-buffering lactate- and cellulose-based gels (37, 50). A newer vaginal pH regulating gel containing lactic acid, citric acid, and potassium bitartrate (Phexxi) has recently come on the market and works to inactivate sperm by maintaining an acidic vaginal environment even in the presence of alkalinic sperm (51). Despite their availability and theoretical efficacy, barrier methods have been associated with a relatively high pregnancy rate of 11 pregnancies/100 women per year, emphasizing the importance of proper usage

Non-Hormonal Contraceptive Methods and Failure Rates

Type	Specific Types	Perfect Use (%)	Typical Use (%)	Relative Cost
 Male Sterilization	Vasectomy	0.1	0.15	$$$$
 Female Sterilization	Tubal Ligation Bilateral Salpingectomy	0.5	0.5	$$$$
 Copper IUD	ParaGard® United States *Several U- and T-shaped Cu-IUDs available worldwide*	0.6	0.8	$$$
 Diaphragm or Cervical Cap (with spermicides)	Diaphragms: Caya®, Milex® Cervical Cap: FemCap™	16	17	$$
 Condoms	Male (external) Condom Female (internal) Condom	2-5	13-21	$
 Spermicides	Foam, Jelly, Cream, or Sponge Detergents, Acid Buffers, Vaginal pH Regulator	16	21	$
 Cervical Mucus	Two-Day Method Billings Ovulation Method	1-4	11-34	ø
 Calendar	Standard Days Method	5	11-14	ø
 Withdrawal	Withdrawal	4	20	ø
 Basal Body Temperature	Natural Cycles Symptothermal	Data Unavailable	2-33	ø

Figure 2. Failure rates and relative costs of nonhormonal contraceptive methods. A list of nonhormonal contraceptive methods with failure rates (defined as % of women who will become pregnant within the first year of use) of perfect vs typical use, as well as their relative costs. From Teal S. and Edelman A. *JAMA*, 2021; 326(24) (37), Genazzani AR et al *Gynecol Endocrinol*, 2023; 39(1) (39), Guttmacher Institute, 2020 (52), & Buhling KJ et al *Contraception*, 2014; 89(3) (53). Created in BioRender. Zaman, A. (2024) BioRender.com/j21x419.

and consistent compliance (37). Figure 2 shows the effectiveness of different nonhormonal contraceptive options by perfect use and typical use (37, 39, 52, 53).

Surgical or procedural methods

The other main form of contraception available to men is vasectomy. This permanent method of contraception entails ligating the vas deferens to prevent sperm from entering semen and takes approximately 3 months to take full effect. Reported vasectomy failure rates—defined as the presence of motile sperm in the ejaculate 6 months postoperatively—range from 0.3% to 0.9%, with an exceptionally low late failure rate of 0.04% to 0.08% (54). Though reanastomosis of the vas deferens with microsurgery can sometimes be done to reverse a vasectomy, restoration of fertility may not reach 100% as men can develop antisperm antibodies that render them infertile even if the vas deferens is reapproximated (11, 55).

In females, permanent contraceptive options originally included tubal ligation (interrupting continuity of the fallopian tubes via cutting, tying, clipping, or cauterizing both tubes) and Essure (a hysteroscopic tubal occlusion method), though the latter procedure is no longer available (56, 57). Bilateral salpingectomy (removal of the fallopian tubes) is a form of tubal ligation and the main female permanent contraceptive used today, though tubal ligation methods remain efficacious and often performed in the United States immediately postpartum. Neither bilateral salpingectomy nor other forms of tubal ligation are superior in overall clinical outcomes to date but are under active investigation (58). All female permanent contraceptive options prevent an ovulated egg from reaching the uterine lining for gestation, with salpingectomy additionally providing an ovarian cancer prevention benefit due to the removal of the fimbriated end of the fallopian tubes (59, 60). The overall pregnancy rate with permanent sterilization is <1 per 100 women per year, though there is a slightly higher risk for ectopic pregnancy within the first 5 years after surgery if contraceptive failure occurs due to the tubal damage (52, 61). Although these methods are considered irreversible, some studies have shown restoration of pregnancy potential after female permanent contraception reversal (62). As tubal reanastomosis is an expensive procedure with suboptimal rates of fertility restoration, most centers now rely instead on in vitro fertilization procedures rather than microsurgery due to cost and effectiveness (62).

Finally, hysterectomy with or without oophorectomy will lead to absolute loss of pregnancy potential. Endometrial ablation or uterine artery embolization for fibroid management are other procedures that may decrease reproductive potential, though do not eliminate the risk of pregnancy completely (63, 64). Counseling regarding the continued use of effective contraception after either procedure is imperative given the high risk of subsequent pregnancies, including many with poor outcomes (65, 66). Regardless, hysterectomy, ablation, and embolization are not considered contraception and are always performed for other medical reasons.

Devices

The ParaGard Cu-IUD is the sole nonhormonal long-acting reversible contraceptive (LARC) device in the U.S., though several types exist internationally (ie, T-shaped vs U-shaped devices that vary in copper dosing) (53). The Cu-IUD is extremely effective in preventing pregnancy with observed rates of 1 pregnancy/100 women per year (37, 67). As an external object placed into the reproductive tract, all IUDs cause a foreign-body reaction consisting of increases in neutrophils, mononuclear cells, and plasma cells (67). The copper ions that are released from the Cu-IUD device amplifies this inflammatory response, rendering the uterine tract inhospitable to sperm. The high amount of copper released into cervical mucus is toxic to spermatozoa and decreases both sperm motility and viability. In addition, copper decreases the proliferation and enzymatic function of endometrial cells (67). Ultimately, the copper IUD reduces chances of both fertilization and implantation. Irregular bleeding and cramping are the common concerns associated with the Cu-IUD, leading to its predominant use in parous women historically. However, acceptability of the Cu-IUD in nulliparous women and adolescents has expanded its applicability, making it a viable option for all reproductive-aged women with contraindications to hormonal contraception (68, 69).

Hormonal Contraceptives

While nonhormonal contraceptives prevent pregnancy by posing anatomical barriers or relying on behavioral changes, hormonal contraceptives work by manipulating the endogenous sex-steroid profile of an individual or through local effects within the female reproductive tract. In combined hormonal contraception (CHC), this is achieved through the administration of exogenous reproductive hormones in supraphysiologic doses that then alter signaling within the HPG axis and block ovulation (70, 71). In addition, the primary objective of hormonal contraception is to impede the normal maturation of gametes, interfere with sperm activity or motility, or thwart implantation of a zygote through either local or systemic actions of a progestin with or without estrogen in females. However, newer research is exploring the potential of incorporating androgens, either alone or in combination with estrogens and/or progestins, for use in males. The role of these hormones in preventing pregnancy are described in greater detail below.

Role of progestins

The backbone of all hormonal contraceptive methods for females is a progestin, which is a synthetic form of naturally occurring progesterone (P4). P4 is a 21-carbon steroid hormone that is predominantly made by the corpus luteum after ovulation, or the placenta in pregnancy. However, P4 cannot be used in hormonal birth control due to poor oral bioavailability and short half-life (72, 73). Synthetic progestins—available in oral, vaginal, subdermal, intramuscular, or subcutaneous formulations—are superior in their metabolism, absorption, distribution, and tissue storage in comparison to P4 and vary in their pharmacologic properties based on the route of administration (74).

Progestins are often classified by their generation (ie, first through fourth) based on their sequence of introduction onto the market, although this method of classification does not correspond to their mechanism of action or side effect profile (73-77). Earlier progestins were derivatives of either P4 or 19-nortestosterone, though the newer drospirenone progestin is derived from spironolactone—a mineralocorticoid receptor antagonist (72). All progestins, analogous to P4, achieve their primary effect through action at the endogenous progesterone receptor. However, the diversity of clinical functions exhibited

Table 1. Progestins used in contraception and their degree of cross-reactivity on other hormone receptors

Progestin[a] (abbreviation)	Derived from	Generation	Androgen receptor[b]	Estrogen receptor[c]	Mineralocorticoid receptor[d]	Glucocorticoid receptor[e]
Strong androgenicity						
Levonorgestrel (LNG)	19-Nortestosterone (Gonane)	2nd	+	–	β	β
Norgestrel (NG)	19-Nortestosterone (Gonane)	2nd	+	–	β	β
Medroxyprogesterone acetate (MPA)	Acetylated Pregnancy	1st	±	–	β	+
Moderate androgenicity						
Norethisterone/ Norethindrone (NET)	19-Nortestosterone (Estrane)	1st	+	+	β	β
Norethindrone acetate (NETA)	19-Nortestosterone (Estrane)	1st	+	+	β	β
Mild Androgenicity						
Gestodone (GST)	19-Nortestosterone (Gonane)	3rd	+	–	–	+
Etonogestrel (ENG)	19-Nortestosterone (Gonane)	3rd	+	–	β	±
Desogestrel (DSG)	19-Nortestosterone (Gonane)	3rd	+	–	β	β
Neutral androgenicity						
Progesterone (P4)	N/A	N/A	–	–	±	±
Segesterone Acetate (SGA)	Progesterone	N/A	β	β	β	β
Moderate antiandrogenicity						
Norgestimate (NGM)	19-Nortestosterone (Gonane)	3rd	+	–	β	β
Norelgestromin (NLGM)	19-Nortestosterone (Gonane)	3rd	+	–	β	β
Dienogest (DNG)	19-Nortestosterone (Estrane)	4th	–	–	β	β
Strong antiandrogenicity						
Drospirenone (DRSP)	Spironolactone	4th	–	–	–	β
Cyproterone Acetate (CPA)	Acetylated Pregnane	1st	–	–	β	+

Commonly used progestins in hormonal contraception compared to natural progesterone listed in order of decreasing androgenicity. Also demonstrated are their cross-reactivities at the androgen, estrogen, mineralocorticoid, and glucocorticoid receptors and their expected agonistic antagonistic clinical effects at the different hormone receptors. Progestin generation is provided to highlight that generation does not indicate similar action or side effect profiles.
+ Positive effect (agonist).
± Weak effect.
β No effect.
– Negative effect (antagonist).
From Schindler AE. *Progestogens in Obstetrics and Gynecology*; 2021 (73), Liu S et al *Curr Opin Obstet Gynecol*, 2022; 34(6) (74), Kuhl H. *Climacteric*, 2005; 8(Suppl 1) (75), & Pletzer B et al *Front Neuroendocrinol*, 2023; 69 (76).
[a]P4 and all synthetic progestins have a positive effect at the progesterone receptor, which limits endometrial proliferation and thickens cervical mucus
[b]Androgen receptor effect: acne, hirsutism, worsens high-density lipoprotein.
[c]Estrogen receptor effect: hypercoagulability, expansion of endometrial tissue.
[d]Mineralocorticoid receptor effect: salt and water retention, elevation of blood pressure.
[e]Glucocorticoid receptor effect: immunosuppression, weight gain, decrease bone mineral density, decrease glucose tolerance.

by progestins originates from their individual ability (as well as that of their metabolites) to bind to different steroid receptors throughout the body, thereby contributing to their distinct side effect profiles (Table 1). In addition to cross-reactivity at different steroid receptors, progestin action and side effects vary by formulation and route, as these lead to different circulating progestin levels. For example, medroxyprogesterone acetate in a depo suspension reaches a concentration of approximately 7 ng/mL, whereas oral medroxyprogesterone acetate concentration is 1 ng/mL. In comparison, progestin concentrations in CHCs reach between 1 and 2 ng/mL, and levonorgestrel concentration from IUDs is around 0.1 ng/mL (78). Different steroids have been chosen for their use in hormonal contraception based on potency, half-life, metabolism, and side effect profile.

Despite progesterone receptors existing in various non-reproductive tissues (ie, central nervous system and gut), progestins in contraceptives exert their effect through the HPG axis or at the level of the cervix. Within the hypothalamus, the main role of progestin is suppression of gonadotropin releasing hormone (GnRH) followed by luteinizing hormone (LH), preventing the mid-cycle LH surge and ovulation (Fig. 3) (70, 79-85). This progestin effect on gonadotropins occurs when progestins are available in supraphysiologic doses—such as in oral, transvaginal, transdermal, or subdermal formulations—and work systemically (81). Intrauterine progestins have a lower systemic effect and act through prolonged local effects within the female reproductive tract to prevent fertilization (86). Specifically, progestins cause thickening of cervical mucus and block sperm penetration into the uterus (87). Moreover, they decrease fallopian tube cilia motility, number, and action, resulting in slowed transport of an ovum and diminishing sperm migration once within the female reproductive tract (87). Endometrial thickness may also progressively decrease depending on progestin treatment duration, reducing the chances of implantation should conception occur, and potentially leading to the cessation of menses over time (88-90). Lack of menses is reversible and should not be of concern to patients and providers. It is also important to reassure women that hormonal contraception will not reduce egg count. Providers should have a discussion about future fertility plans and could potentially offer measurement of anti-Müllerian hormone levels before hormonal contraception initiation to glean a sense of active ovarian reserve follicle

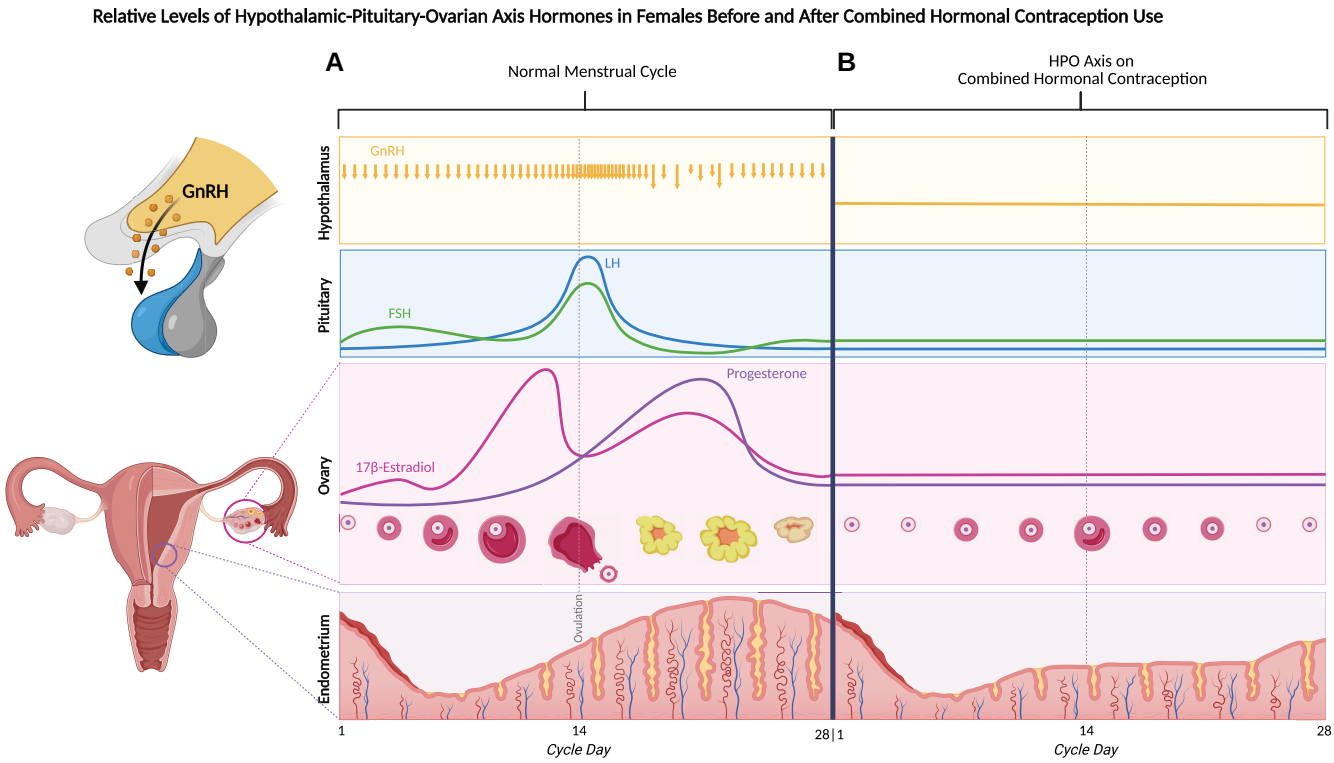

Figure 3. Relative levels of hypothalamic-pituitary-ovarian axis hormones in females before and after hormonal contraception use. Hypothalamic-pituitary-ovarian (HPO) axis in females over a typical, 28-day menstrual cycle under (A) normal conditions and (B) once combined hormonal contraception (CHC) is started. The first day of bleeding is considered day 1, and in a normal menstrual cycle (A), is signified by low levels of endogenous estradiol (E2), endogenous progesterone (P4), and pituitary gonadotropins (FSH and LH). As the cycle progresses, GnRH causes the release of FSH, which in turns leads to ovarian follicular development, E2 secretion, and endometrial thickening. As E2 continues to rise and the follicle develops, positive feedback on the hypothalamus speeds up GnRH pulsatility and ultimately leads to the LH surge and ovulation. The corpus luteum then secretes high amounts of P4 to prepare for potential pregnancy. However, if this does not occur, the endometrial lining is shed, signifying the start of the next menstrual cycle. If a CHC is started (B), supraphysiologic levels of ethinyl estradiol (EE) and a progestin suppress endogenous E2 and P4 through negative feedback of GnRH, FSH, and LH. This prevents follicular maturation and ovulation. Progestins also cause thickening of cervical mucus to inhibit sperm penetration into the uterus. Follicles are arrested in earlier phases (though their phase and size depends on the dose of EE in the CHC). Due to endogenous suppression of the HPO axis from the CHCs, the endometrial lining remains thin. If the inactive CHC is taken at the end of the pack as directed by many manufacturers, there is a slight thickening of the endometrium toward the end of the CHC-controlled cycle, as depicted by the minimal rise of the endometrium at the end of panel B. This is then shed, signaling the start of the next menstrual cycle. From Marques P et al *Endotext*, 2022 (79), Montoya ER and Bos PA. *Trends Cogn Sci*, 2017; 21(2) (80), Lovett JL et al *Evol Med Public Health*, 2017; 2017(1) (81), Fleischman DS et al *Psychol Sci*, 2010; 21(5) (82), Baerwald and Pierson RA. *J Obstet Gynaecol Can*, 2004; 26(1) (83), ESHRE Capri Workshop Group. *Hum Rep*, 2001; 16(7) (84), & Crowley WF et al *Recent Prog Horm Res*, 1985; 41 (85). Created in BioRender. Zaman, A. (2025) https://BioRender.com/k59b743.

(not fertility potential) (91). Regardless of formulation, route, or duration of progestins used in hormonal contraception, return of fertility occurs at similar rates after discontinuation of the various hormonal contraceptive methods (92). One caveat is with depot medroxyprogesterone acetate (DMPA), as return of fertility may be delayed for up to 18 months after discontinuation, even after receiving only 1 dose (93, 94).

Building on the mechanisms of progestins in female contraception, their application extends to male alternatives. Similar to progestin effects in females, progestins in male contraception work as a major adjunct to testosterone to suppress gonadotropins and ultimately spermatogenesis (95). However, the lowest effective progestin dose has yet to be determined, and only 2 male contraceptive methods composed of steroids with progestational activity have made it into clinical trials (7). This is described in more detail in the following.

Role of estrogens

The addition of estrogen in contraceptive methods offers several key advantages, including stabilization of the endometrium, minimization of breakthrough vaginal bleeding, and reduction of follicle development by suppressing FSH in the pituitary (96). Additionally, estrogens play a crucial role in upregulating hepatic estrogen-sensitive proteins, such as sex-hormone binding globulin (SHBG), ultimately decreasing the levels of biologically active androgens in circulation (97). It is important to note that estrogens should always be used in conjunction with a progestin due to an increased risk for endometrial hyperplasia and cancer with unopposed estrogen therapy in females with an intact uterus (98). Estrogens are utilized alone in females without a uterus for hormone replacement therapy in menopause and not for contraception.

Unlike the wide variety of progestins that are available for use in hormonal contraceptives, there have only been 3 different estrogens introduced into the US market in oral contraceptive pills since 1961. 17β-Estradiol (E2) is the physiologically produced estrogen by the human ovarian granulosa cells but is not the major form used in current birth control methods. The first estrogen used in the original oral contraceptive pill to hit the US market (Enovid) was mestranol. Initially thought to be a contaminant when developing the progestin in Enovid, elimination of mestranol led to unacceptable bleeding patterns and

was therefore added back into Enovid's formulation (99). Mestranol is metabolized into the more potent, active ethinyl estradiol (EE). EE therefore quickly became the predominant synthetic estrogen used in hormonal contraception due to its stability (100). In comparison, E2—though the most post potent of the naturally occurring estrogens—has poor absorption and half-life when included in oral formulations (101). Additionally, EE is equivalent to a 4-fold dose of E2 in part because it is less rapidly metabolized (102). The issue is further confounded by the fact that EE has markedly higher potency compared to E2, allowing for lower doses of EE to achieve equivalent results, with the actual estrogenic activity of a smaller EE dose being greater than that of E2.

Despite multiple efforts to introduce an E2-containing contraceptive method, only 1 such birth control option exists globally (nomegestrol acetate 2.5 mg/17β estradiol 2.5 mg [Zoely]), currently unavailable in the United States (103). E2 has also been esterized to create the pro-drug estradiol valerate (E2V), which is used in combination with the progestin dienogest with similar contraceptive efficacy and side effect profiles to common EE-containing contraceptive pills (97, 101, 104). The newest estrogen to become commercially available is estetrol (E4), which is a naturally occurring estrogen produced by the fetal liver (105). Unlike EE and E2, E4 acts more akin to a selective estrogen receptor modulator because it has differential estrogen receptor-binding properties in different human tissues. E4 is only available in a single combined oral contraceptive pill formulation in the United States, which we discuss in more detail in the novel contraceptive method section of this review.

As with progestins, the relative potency of various estrogens varies by tissue specific effects, route of administration, and half-life. The differences in these parameters between E2, EE, E2V, and E4 are covered in extensive detail in a recent review article by Stanczyk et al (106), but in brief, E2 has a 13- to 20-hour half-life with low bioavailability and significant metabolism. Though E2V has similar characteristics to E2, it has more stable pharmacokinetics. EE has the highest potency and hepatic effects, with a half-life of 5 to 30 hours, and E4—the weakest estrogen—has a longer half-life (~28 hours) and better bioavailability (106). In general, oral delivery of estrogens has a stronger impact on the liver despite lower overall blood levels (ie, area under the curve [AUC]) compared to transdermal forms, which provide a steadier release and higher total exposure over time (107).

Role of testosterone

While not utilized directly within hormonal contraceptive options, androgens served as one of the precursors from which the earliest progestins were derived. Testosterone is a steroid hormone that exerts its effects in the body through androgen receptors. While not the only androgenic steroid present in humans, testosterone is made primarily by the ovaries in small amounts in females and by testicular Leydig cells in males. As the primary reproductive hormone in males, high-dose testosterone was first shown to lead to oligospermia (<15 million sperm/mL ejaculate) in the 1930s, but garnered interest as a potential male contraceptive option in 1972 (108, 109). When given exogenously to a male patient with a normal HPG axis, testosterone suppresses GnRH and the pituitary gonadotropins, which then decreases intratesticular testosterone levels, interferes with spermatogenesis, and results in oligospermia (Fig. 4) (7, 85, 110-114). Studies to date evaluating administration of exogenous testosterone options for male contraception have demonstrated good acceptability and resumption of spermatogenesis after treatment cessation through return of normal LH and follicle stimulating hormone (FSH) secretion and intratesticular testosterone concentrations (111). However, acceptability and efficacy trials have resulted in unsatisfactory rates of nonsuppressed spermatogenesis or lack of compliance, preventing FDA approval and availability thus far. Details of such trials have been summarized in recent reviews (111, 115).

Combined Hormonal Contraceptive Methods

CHC methods—which include the combined oral monophasic or multiphasic contraceptive pill (COCP) with conventional or extended delivery options, the transdermal patch, or the vaginal ring—are the most prevalently used hormonal contraceptive methods among premenopausal women globally (116-118). Most CHC methods contain a static dose of both an estrogen and progestin, while multiphasic COCPs have a step-up in the doses of progestin to theoretically mimic the menstrual cycle. There are no differences in their efficacy to prevent fertility or side effect profiles; however, multiphasic COCPs may result in more intermenstrual bleeding if not taken at the same time each day (119-121). Any COCP can be used continuously to reduce the number of menstrual cycles per year with only some formulations receiving specific FDA approval for this purpose (Table 2).

Earlier CHCs included 7 days of placebo at the end of a monthly pack but newer CHCs have reduced placebo windows of 2 or 4 days. Effectiveness of hypothalamic-pituitary-ovarian suppression, escape ovulation, and endometrial proliferation leading to breakthrough bleeding causing dissatisfaction and/or nonadherence are all considerations in the design. Given that recovery of ovarian function can occur within day 3 to 5 of the placebo window (123), it is increasingly recommended to limit the placebo window to no more than 4 days with pill formations as this improves efficacy without significantly affecting bleeding profiles compared to a 7-day placebo period (124). From an efficacy standpoint, continuous use of CHCs is associated with the highest contraceptive effectiveness and also confers high patient satisfaction in controlling cycles (125). While long-term use of CHCs has been shown to confer a protective association for ovarian and endometrial cancers, data on the difference in lifetime risk of breast cancer is unknown between traditional 7 days of placebo or continuous CHC use (126, 127). Adolescent women using CHCs had less bone accrual compared to control (128, 129); however, low-dose estrogen and progestin provides no contraception and irregular bleeding may ensue.

Beyond considering the efficacy of a CHC method, the extensive array of commercially available products often complicates the provider's decision-making process in selecting a hormonal contraceptive option for patients. For instance, in addition to the multitude of available COCPs, combinations of EE with various progestins are also offered in weekly combination patches and monthly or yearly vaginal rings. In a Cochrane review of 18 trials assessing the transdermal patch and vaginal ring, the norelgestromin contained in one of the monthly patches was associated with more breast discomfort,

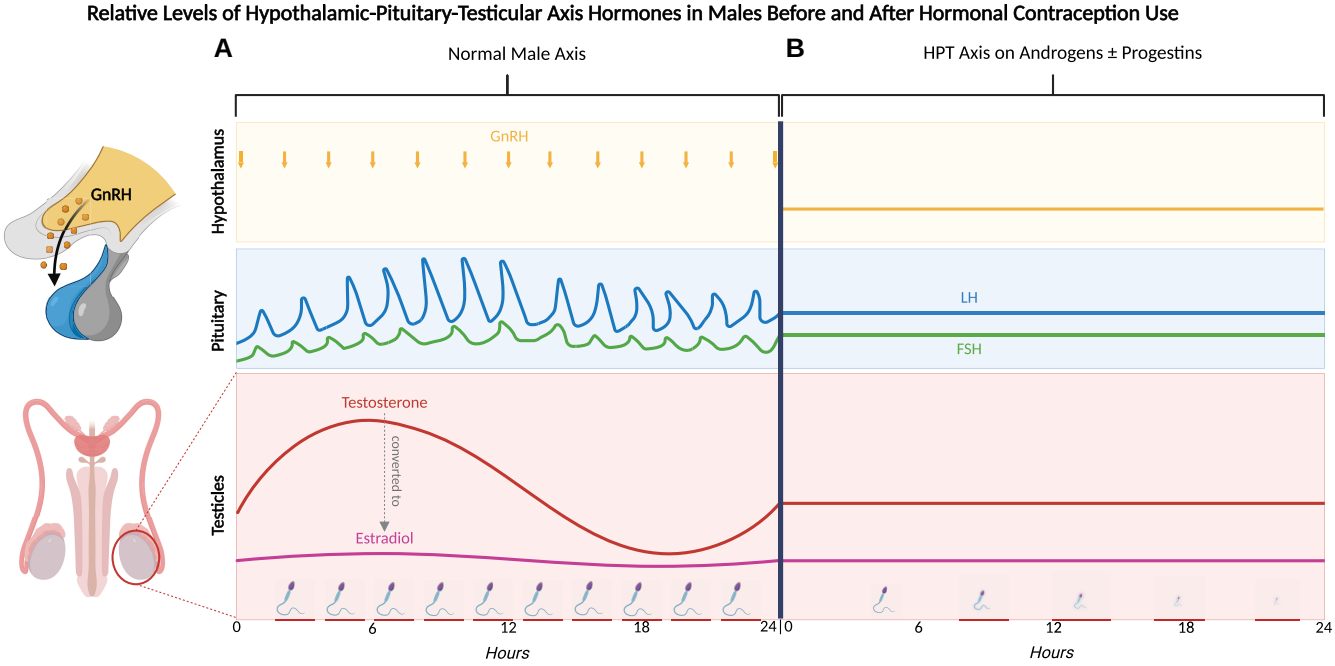

Figure 4. Relative levels of hypothalamic-pituitary-testicular axis hormones in males before and after hormonal contraception use. Hypothalamic-pituitary-testosterone (HPT) axis in adult males with normal fertility potential over a 24-hour period during (A) normal conditions and (B) once hormonal contraception is started. After puberty, GnRH is consistent across the day and supports gonadotropin—LH and FSH—secretion. While FSH is secreted in stable amounts throughout the day, LH pulsatility increases during sleep, which leads to the rise in testosterone. LH amplitude decreases during the awake hours, which accounts for the diurnal pattern of testosterone being elevated in the mornings and falling throughout the day. Testosterone is secreted by the Leydig cells of the testes and is converted into estradiol, which has a negative feedback action on GnRH, FSH, and LH. Testosterone is also converted in dihydrotestosterone (DHT). Sertoli cells in the testicles support spermatogenesis. Exogenous androgens have been tested in males as a potential contraceptive option and works by suppressing endogenous testosterone levels and suppressing spermatogenesis as depicted in Panel B. When a progestin is added to the androgen, the suppressive effects of testosterone on the HPT axis is potentiated by the additional exogenous hormone. From Crowley WF et al *Recent Prog Horm Res*, 1985; 41 (85), Brambilla DJ et al *J Clin Endocrinol Metab*, 2009; 94(3) (110), Thirumalai A and Page ST. *Annu Rev Med*, 2020; 71 (111), Seminara SB et al *Endocr Rev*, 1998; 19(5) (112), Marshall JC and Kelch RP. *N Engl J Med*, 1986; 315(23) (113), & Wildt L et al *Endocrinol*, 1981; 109(2) (114). Created in BioRender. Zaman, A. (2025) https://BioRender.com/e48m081.

painful periods, nausea, and vomiting (130). The etonogestrel progestin found in the vaginal ring was associated with more vaginal irritation and discharge, but less nausea, acne, depression, or mood issues. Additionally, the vaginal ring may result in a higher overall exposure to estrogen than the transdermal patch, though both the vaginal ring and patch avoid the EE peaks found with COCPs (107, 131). Yet, there remain few prospective, controlled studies comparing these products.

With the introduction of contraception containing lower doses of EE or newer progestins, the medical field's understanding of contraindications to CHC methods has evolved (132, 133). Though CHC methods were not initially prescribed to women with a higher body mass index (BMI), overweight or obesity do not appear to have an increased risk of contraceptive failure (134). The one exception is with the levonorgestrel/ethinyl estradiol patch (Twirla), which carries a black box label for patients with a BMI $\geq$30 kg/m^2 due to decreased efficacy (135, 136). There also exists a concern for increased hypercoagulability or cardiovascular risks with CHC use in those with obesity (137). An exhaustive list of contraindications to CHCs is available within the Centers for Disease Control and Prevention's (CDC) 2016 US Medical Eligibility Criteria for Contraceptive Use (133). Commonly known contraindications include age older than 35 years, smoking, uncontrolled hypertension, a history of breast cancer or cardiovascular disease, migraines with aura, and prolonged immobilization (138). Liver or gallbladder disease present weaker contraindications. Additionally, women with a clotting disorder, recent venous thrombotic events (VTE), or pulmonary embolism should avoid all estrogen-containing hormonal contraception. However, for patients on long-term therapeutic doses of anticoagulation, the consideration of a low-dose CHC may be an option (139). The CDC strongly recommends against screening for thrombophilias prior to the initiation of CHCs unless in the absence of a preceding VTE event (133). CHC methods remain contraindicated in those on anticoagulation for VTE prophylaxis only.

This cautionary approach is due to the recognized risk of VTE associated with estrogen-containing contraception. Over time, efforts to mitigate this risk—among others associated with prolonged high estrogen exposure—have involved progressively reducing the dose of EE (the most commonly used estrogen in CHC methods) from 50 to 100 μg in earlier formulations to 10 to 35 μg in contemporary CHC methods. More recently, COCPs containing E2 or E4 as the estrogenic component have become available, which claim to be less thrombogenic than EE based on pharmacological properties and hemostatic markers, but more real-world data are needed to substantiate these claims (38, 39, 77). VTE rates have remained relatively stable among CHC users since the standard EE dose was decreased to 10 to 35 μg, but a small absolute increase in VTE rates have been noted with more recent CHC formulations, such as those containing drospirenone. This small increase in VTE risk is likely due to the use of progestins with lower

Table 2. Combined hormonal contraceptive methods and failure rates

Type	Specific types				Perfect use (%)	Typical use (%)
	Progestin	Estrogen	Dosing progestin/ estrogen	Brand name(s)		
Oral	LNG	EE	0.1 mg/20 µg	Aubra, Aviane, Delyla, Falmina, Falessa, Larissia, Lessina, Lutera, Orsythia, Vienva	0.3	7
			0.15 mg/30 µg	Altavera, Amethia[a], Ashlyna[a], Camrese[a], Chateal, Daysee[a], Jaimiess[a], Kurvelo, Levora, Lillow, Marlissa, Nordette, Portia, Seasonique[a]		
			0.09 mg/20 µg	For Continuous Use: Generic Only.		
	NG	EE	0.3 mg/30 µg	Cryselle, Elinest, Lo-Ogestrel, Lo-Ovral		
			0.5 mg/50 µg	Ogestrel		
	NET	EE	0.4 mg/35 µg	Balziva-28, Briellyn, Gildagia, Philith, Rhuzdah, Vyfemla, Zenchent		
			0.5 mg/35 µg	Cyclafem, Cyonanz, Modicon, Necon, Nortrel, Wera		
			1 mg/35 µg	Alyacen, Brevicon, Cyclafem, Dasetta, Necon 1/35, Norinyl, Nortrel 1/35, Nylia, Ortho Novum, Pirmella		
			1 mg/50 µg	Brevicon		
	NETA	EE	1 mg/20 µg	Larin 1/20, Loestrin 1/20, Microgestin 1/20, Junel 1/20		
			1.5 mg/30 µg	Hailey, Larin, Loestrin, Microgestin, Junel		
	GST[b]	EE	0.075 mg/30 µg	Femodene, Minulet		
	DSG	EE	0.15 mg/30 µg	Apri, Cyred, Desogen, Emoquette, Enskyce, Isibloom, Juleber, Ortho-Cept, Reclipsen, Solia		
	NGM	EE	0.25 mg/35 µg	Estarylla, Femynor, Mili, Mononessa, Previfem, Sprintec		
	DNG	EE	2 mg/30 µg	Elogen[b], Freedase[b], Sibilla[b]		
		E2V	*Quadriphasic* 1-3 mg/2-3 mg	Qlaira[b], Natazia		
	DRSP	EE	3 mg/20 µg	Beyaz, Gianvi, Loryna, Vestura, Yaz		
			3 mg/30 µg	Ocella, Safyral, Syeda, Tydemy, Yaela, Yasmin, Zarah,		
	CPA[b]	EE	2 mg/35 µg	Diane-35[c]		
		E2V	1 mg/2 mg	Climen, Femilar		
Transdermal	LNG	EE	0.12 mg/30 µg	Twirla	0.3	7
	NLGM	EE	0.15 mg/35 µg	Xulane		
Vaginal	ENG	EE	0.12 mg/15 µg	NuvaRing, EluRyng	0.3	7
	SGA	EE	0.15 mg/13 µg	Annovera		

A list of combined hormonal contraceptive methods with failure rates (defined as % of women who will become pregnant within the first year of use) of perfect vs typical use in order of decreasing androgenicity. There is an overwhelming number of options when selecting a CHC but the failure rate of perfect vs typical use does not differ based on progestin or estrogen type, dosing, or route. Of greater importance to the endocrinologist prescribing a CHC are the goals of the patient with endocrine disorders as well as the potential side effect profile of the medication. Formulations where either the progestin or the synthetic estrogen dose changes throughout the blister pack are not depicted as contraceptive efficacy and side effect profiles do not differ between monophasic vs bi- or triphasic pills.

Abbreviations: CHC, combined hormonal contraception; CPA, cyproterone acetate; DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; E2V, estradiol valerate; EE, ethinyl estradiol; ENG, etonogestrel; GST, gestodene; LNG, levonorgestrel; NET, norethindrone; NETA, norethisterone acetate; NG, norgestrel; NGM, norgestimate; NLGM, norelgestromin; SGA, segesterone acetate.

From Teal S. and Edelman A. *JAMA*, 2021; 326(24) (37), Genazzani AR et al *Gynecol Endocrinol*, 2023; 39(1) (39), Guttmacher Institute, 2020 (52), & Barton BE et al *Biol Reprod*, 2024; 110(1) (122).

[a]FDA approved to be used for days 1-84 as opposed to a days 1-21 schedule to induce a monthly menses.

[b]Not available in the United States.

[c]No longer available in the United Kingdom or North America. CPA has also been significantly limited in many European countries. However, an oral contraceptive pill containing CPA with EE is available under several more names throughout the world.

androgenicity or those that are actually antiandrogenic (140). There are no definitive data to explain which pharmacokinetic factors (ie, AUC vs peak levels) lead to increased VTE risk, but the limited evidence available supports peak estrogen exposure over AUC as being more significant (141). Progestins with moderate-to-high androgenicity can counteract some of the hematological changes that occur with EE exposure, thus resulting in slightly lower VTE risk with CHC formulations containing levonorgestrel and norethindrone (140). The 1 exception to this theory was with norgestimate (a moderately antiandrogenic progestin), likely due to its partial conversion to levonorgestrel (a moderately androgenic progestin) (140). Norethisterone and norethindrone are also metabolized in part to estrogenic compounds and thereby exert an effect on estrogen receptors (Table 1) (142), although the clinical implications for risks such as VTE have been mixed. For example, Cockrum et al found that the norethindrone progestin-only pill was protective against VTE, but a higher dose of norethindrone acetate was associated with higher VTE risk (143). The overall VTE risk of different CHC formulations is based on its overall estrogenicity (ie, the sum of the estrogen and the effects of the progestin on the estrogen receptor) rather than the EE dose directly (144). However, the absolutely differences in VTE risks between CHCs with different progestins are not clinically significant and patients with clinical contraindications to estrogen-containing contraception should avoid CHCs regardless of the progestin used.

The effects of CHCs on mood are variable. Some studies document an increased incidence or worsening of depression with CHC use, with some postulation that it depends on the type, potency, and duration of exposure to the progestin (145). There are association studies, but little available prospective, placebo-controlled studies on the absolute risks. In contrast, other studies have demonstrated a significant improvement in premenstrual dysphoria with CHCs and have argued for a shorter placebo period to avoid worsening mood effects (146, 147). Among women with polycystic ovary syndrome (PCOS), there is strong evidence to support the high prevalence of anxiety and depression. The 2023 International PCOS Guidelines recommend CHCs as a first-

Table 3. Progestin only contraceptive methods and failure rates

Type	Specific types			Perfect use (%)	Typical use (%)
	Progestin	Dosing	Brand name(s)		
Implant	LNG ENG	75 mg × 2 68 mg	Jadelle[a], Sino-Implant[a] Nexplanon	0.1	0.1
Injectable	D-MPA	104 mg 150 mg	Depo-SubQ Provera Depo-Provera	0.2	4
IUD	LNG	13.5 mg 19.5 mg 52 mg	Skyla Kyleena Mirena, Liletta	0.1-0.3	0.1-0.4
Oral	NG NET DSG DRSP	0.075 mg 0.35 mg 0.075 mg 4 mg	Opill Camila, Deblitane, Emzahh, Errin, Heather, Jencycla, Nor QD, Ortho Micronor, Sharobel Lovima[a], Hana[a] Slynd	0.3	7

A list of progestin-only contraceptive methods with failure rates (defined as % of women who will become pregnant within the first year of use) of perfect vs typical use in order of decreasing androgenicity. An LNG-only pill exists but is used solely as emergency contraception (Plan B®).
Abbreviations: D-MPA, depot medroxyprogesterone acetate; DRSP, drospirenone; DSG, desogestrel; ENG, etonogestrel; LNG, levonorgestrel; NET, norethindrone; NG, norgestimate.
From Teal S. and Edelman A. *JAMA*, 2021; 326(24) (37), Genazzani AR et al *Gynecol Endocrinol*, 2023; 39(1) (39), Guttmacher Institute, 2020 (52), & Barton BE et al *Biol Reprod*, 2024; 110(1) (122).
[a]Not available in the United States.

line therapy for managing hyperandrogenic and menstrual symptoms, despite limited data on mood in this population (148). There has been only one prospective observational study of 36 women with PCOS without psychiatric diagnoses found no significant changes in depressive or anxiety symptoms after 6 months of CHC use (149). Given the current gaps in high-quality, controlled evidence, clinicians are urged to monitor all patients using CHCs for changes in mood and to tailor contraceptive choices accordingly.

Taken together, all of these CHCs have a pregnancy rate of 4 to 7 pregnancies/100 women per year with typical use, though perfect use rates demonstrate >99% effectiveness (Table 2) (37, 39, 52, 122). They also result in lighter, shorter episodes of menstrual bleeding, often improve cramping and premenstrual syndrome symptoms, and, in the case of CHC methods containing more antiandrogenic progestins, aid in the treatment of hirsutism and/or acne (150). Couples interested in fertility should note the slight delay that may occur after CHC use, though synthetic hormones are cleared within 7 days, with fertility typically returning immediately afterward and most women achieving pregnancy within a year of CHC discontinuation (75, 92, 151).

Progestin-only Contraceptive Methods

Though the first hormonal birth control option was a COCP, progestin-only methods have been prioritized in recent years, especially in nonoral forms (37, 39). This is in part due to the rising number of women with overweight/obesity or other medical comorbidities who may have a higher risk of adverse effects with estrogen-containing contraceptives (152, 153). Progestin devices, the only hormonal methods used in LARCs, include 4 levonorgestrel IUDs: Mirena (52 mg/device), Liletta (52 mg/device), Kyleena (19.5 mg/device), and Skyla (13.5 mg/device) (122). IUDs are highly effective birth control options with a failure rate of less than <1 pregnancy/100 women per year (Table 3) (52). Women using levonorgestrel IUDs typically note a decrease in menstrual bleeding. Although the systemic absorption of levonorgestrel in the IUD is low, some women experience an increase in androgenic symptoms, likely from the high androgenicity of levonorgestrel (86). Regardless, the hormonal IUDs are useful in decreasing heavy bleeding, treating primary dysmenorrhea, adenomyosis, and endometriosis. They also protect from pelvic infections (28).

Subdermal implants—another form of progestin-only LARCs—previously included Norplant (levonorgestrel 216 mg/device) and Implanon (etonogestrel 68 mg/device), but Nexplanon (etonogestrel 68 mg/device) and Jadelle or Sino-Implant (both containing levonorgestrel 150 mg/device) are the only implants available worldwide today. Norplant was completely phased out of the US market by 2004 due to possible ineffectiveness, though testing did not show an impact on contraceptive efficacy from lower progestin release rate (27). In contrast to the controversy surrounding Norplant, Implanon was replaced by Nexplanon in 2010 because of its easier insertion and localizability on x-ray scans for extraction (154). Implants can offer many of the same noncontraceptive benefits as IUDs and has popularity particularly among adolescents and younger populations (39, 155). In addition, the etonogestrel-containing implants may have fewer androgenic side effects compared to levonorgestrel. Abnormal bleeding patterns have been cited as one of the most common reasons for discontinuation of etonogestrel implants and some studies have shown improvement in bleeding when exogenous estradiol (in the form of a COCP) was added (156, 157). However, these benefits quickly reversed once the exogenous estradiol was stopped. However, no head-to-head studies comparing these 2 progestins have been performed (156). Implants are similarly effective to IUDs with a pregnancy rate of <1 pregnancy/100 women per year, making their efficacy close to permanent methods (Table 3) (37, 39, 52, 122).

In addition to IUDs and implants, DMPA is a progestin-only injection that is administered every 3 months for contraception (37, 39). There are 2 contraceptive formulations of DMPA that are administered every 3 months and work similarly: DMPA 150 mg (Depo-Provera) is an intramuscular injection administered to patients in clinic whereas DMPA 104 mg (Depo-SubQ Provera) can be subcutaneously self-injected by the patient (158). Medroxyprogesterone acetate is also available orally

for the management of abnormal uterine bleeding or endometrial hyperplasia but not approved for contraception. DMPA is highly effective with a failure rate of 1 pregnancy/100 women per year (Table 3). Although the high dose of medroxyprogesterone acetate in DMPA is necessary to effectively inhibit ovulation, it also suppresses E2, causing bone loss. Additionally, its interaction with glucocorticoid receptors can lead to insulin resistance, weight gain, hirsutism, and acne in some individuals, increasing the risk of discontinuation (75, 159-161). A recent review of all available progestin-only contraceptives containing high doses of progestins have additionally raised concerns that oral norethindrone acetate and DMPA may increase VTE risk, which should be taken into consideration with counseling patients with other medical comorbidities that likewise increase VTE risk (eg, hypertension, smoking, thrombogenic mutations) (143).

Progestin-only pills (POPs: norethindrone, levonorgestrel, drospirenone, desogestrel, and norgestrel) have not garnered the same popularity as COCPs primarily because of concerns about efficacy with timing of ingestion. Contraceptive counseling with POP use has focused on the manufacturer's recommendation (norethindrone 0.35 mg [Micronor]) that the pill needs to be taken within the same 3-hour window every day to maintain adequate cervical mucus thickness (162). However, this advice was based off a 1968 study on 6 women using megestrol acetate—a progestin that is no longer available for use by humans—as well as the known pharmacokinetics of norethindrone, which is nearly metabolized within 24 hours (89, 163). Though the necessity of the 3-hour window has been called into question, certain POPs such as drospirenone 4 mg (Slynd) retain contraceptive efficacy even with missed dosing (164). This is in part due to the relative higher doses of drospirenone in POPs as compared to norethindrone. Desogestrel POPs are similarly higher in relative progestin dosing and do not have a strict dosing window. However, other POPs, such as levonorgestrel or norgestrel, do need daily administration within a specific window to retain efficacy given their relatively lower dose of progestin (75). Studies on the differential androgenic side effects of the various POPs are not well established.

There are certain populations of women for whom estrogen is contraindicated, making progestin-only birth control options an obvious choice for contraception. For example, lactation is inhibited by estrogen through its feedback and suppression of prolactin, which is necessary for milk production. Though lactation is suppressed during pregnancy by high levels of progesterone secreted by the placenta, progestin-only contraceptive options can be used postpartum as the levels of synthetic progestin is far lower than circulating levels in pregnancy and does not inhibit milk supply (165). However, the foremost reason that estrogen-containing contraception is contraindicated in the initial (first 4-6 weeks) postpartum period is due to the higher risk of VTEs after parturition, supporting the use of progestin-only contraceptives in this time frame (166).

Other instances where a POP might be preferred over a CHC for women seeking pill therapy are those at higher risk of VTE, as estrogen concentrations have been directly correlated with VTE risk (122). Moreover, women with prior estrogen-related cancers are also counted among those in whom estrogen therapy is contraindicated and a progestin-only method is preferred (167). Though migraine with aura was historically a contraindication to CHC use due to increased stroke risk with estrogens, this has recently been called into question with modern CHC methods containing less than 0.02 mg EE that may help reduce the frequency of menstrual migraines and aura (168). To meet the growing need for more accessible progestin-only contraceptive methods, 2 desogestrel 0.075 mg POPs (Lovima, Hana) have been available without a prescription in the United Kingdom since 2021 and the norgestrel 0.075 mg oral tablet (Opill) was recently approved for over-the-counter purchase in the United States in July 2023 (89, 122, 169). When assessing efficacy, POPs are often combined with COCPs due to a smaller number of POP users in comparison to COCP users, and therefore are reported to have similar pregnancy rates (ie, pregnancy rate up to 9 pregnancies/100 women per year) (37, 52). Side effects of breakthrough bleeding with progestin-only contraception can be obviated by administration of low-dose estradiol patch in those whom estrogens are not contraindicated.

Postcoital Contraceptives

Although prescribing EC, or postcoital contraception, generally falls outside of the scope of practice for endocrinologists, they remain noteworthy. EC aims to prevent pregnancy after unprotected (or underprotected) sexual intercourse but before implantation occurs (170). The fertile window in females spans approximately 6 days (5 days preovulation to 1 day post-ovulation), during which EC works to prevent ovulation or fertilization. A 2023 review by Rudzinski et al extensively covers the mechanism of action, side effects, and other clinical considerations for the available EC worldwide (171). These options include the combined estrogen-progestin pills (Yuzpe method), POPs (levonorgestrel), selective progesterone receptor modulators (ulipristal acetate, mifepristone), and the Cu-IUD. Of these, the Cu-IUD is the most effective if used within 120 hours of intercourse, with delayed insertion still decreasing chances of pregnancy (170, 172). The Cu-UD interrupts fertilization by inducing chemical changes in the sperm and egg before conception, and also by provoking an inflammatory response in the uterus to decrease endometrial receptivity (34). In contrast, selective progesterone receptor modulators impact gonadotropins to decrease ovulation or negatively impact the endometrium (171). As described earlier in this text, estrogens and progestins in oral forms work on the HPG axis to disrupt folliculogenesis. With the exception of Cu-IUD and mifepristone, all EC works to prevent ovulation and have reduced efficacy if given postovulation. It is therefore important to note that EC does not induce abortion as they cannot interrupt an established pregnancy or harm a developing embryo (173).

Summary of Hormonal Contraceptives

Overall, hormonal birth control options containing estrogen plus a progestin offer a range of desirable effects, including regular menstrual cycles, reduced cramping, and potential control of hyperandrogenic symptoms (ie, acne, hirsutism) depending on the progestin component. In some cases, adding estrogen—typically in the form of an estradiol patch—to a progestin-IUD, implant, or progestin-only contraception—can provide greater ovarian suppression and may improve bleeding patterns or bone accretion in women for whom estrogens are not contraindicated. Progestin-containing implants or IUDs stand out as the most efficacious contraceptive methods, though they can be costly or may not be universally available or accepted. It is crucial to consider the potential for

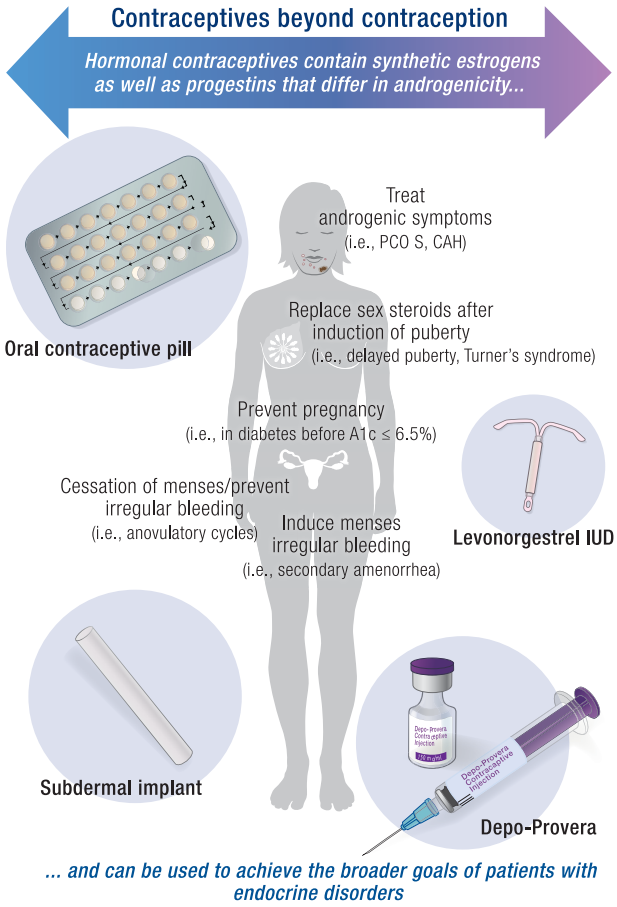

Figure 5. Therapeutic applications of hormonal contraceptives for endocrine and metabolic disorders. Hormonal contraceptives contain synthetic estrogens and progestins that vary in androgenic activity, allowing them to be used for a range of therapeutic indications beyond pregnancy prevention. These include treatment of androgen excess symptoms (eg, hirsutism, acne in PCOS or CAH), induction or regulation of menses (eg, in amenorrhea or anovulatory cycles), prevention of irregular or heavy bleeding, and sex hormone replacement after induction of puberty (eg, Turner syndrome). Hormonal contraceptives may also be used in endocrine conditions where pregnancy is not advised or when optimization of disease control is suggested prior to conception (eg, diabetes with elevated hemoglobin A1c). Route of administration and specific hormone formulation should be selected based on individual patient goals, underlying endocrine pathology, and risk profile. Clinical use of hormonal contraceptives may vary based on patient preference, provider experience, and local practice patterns.

exacerbating hyperandrogenic symptoms, and, in the case of DMPA, abnormal weight gain and depressed mood. Despite the dramatic decrease in EE doses in available products, risks such as VTE, worsening migraines, and hypertension still persist, with causes for discontinuation varying across different product types.

Contraceptives Beyond Contraception

For endocrinologists, choosing the best hormonal contraceptive method for their individual patient involves careful consideration of the various pharmacodynamic actions of exogenous steroid hormones, whether in treating secondary amenorrhea, hyperandrogenism, or during the perimenopausal transition (Fig. 5). Considerations for endocrinologists when suggesting a particular contraceptive option apart from concerns of pregnancy include: the patient goals, whether sex hormone replacement is needed, whether hyperandrogenic symptoms (ie, hirsutism and acne) are to be suppressed, metabolic effects, and mood effects. Unfortunately, there have been few randomized controlled studies of various hormonal contraceptive methods independent of their effectiveness to prevent pregnancies. Another factor to consider is the cost of different contraceptive methods, their availability in different health care systems compared to generic versions, or accessibility. Table 4 provides example patient cases and suggestions on a type of contraception that may be used to achieve specific patient treatment goals. However, there are many options for contraception selection beyond what is stated in Table 4 as practice patterns or preferences can differ significantly between patients and medical providers globally. Many of the following scenarios involve patients with altered hormonal status and reproductive axis for which CHCs can be given. However, if the CHC is stopped, the underlying process is not cured but rather persists and would need to be addressed based on patient goals. Additionally, it often takes a variable period of time for ovulatory cycles to resume after stopping CHCs, and if this period is prolonged, it may indicate an underlying defect requiring further evaluation (174).

Puberty or Transsex Hormones

To induce puberal development and female secondary sex characteristics in a cis- or transwoman, estradiol or other estrogens are given alone in a staircasing fashion for breast development (175, 176). Supraphysiologic doses of estrogen are needed for optimal breast development in transwomen because of the intact male gonad, though these high levels of estrogens increase the risk of deep vein thrombosis (177). A cohort study of almost 5000 transwomen matched with cisgender controls documented a 3.4 and 13.7 per 1000 persons risk at 2 and 8 years (178). During puberty induction for either a transwoman or transman, a GnRH analogue can be used to suppress endogenous gonadal function, allowing for reduced doses of estrogens or androgens, respectively, to achieve desired secondary sex characteristics (179). Available in monthly, 3-month, and now oral formulations (180), this option may confer lower side effect risk of sex hormone replacement. As cost and availability of GnRH analogs remain a barrier, patients may opt to pursue gonadectomy. When the testes are removed in transwomen, for example, estrogen doses can be decreased to mimic physiologic levels in cis-women. After achieving maximal breast development, progesterone can be added to differentiate the ductules. In cis-women, the addition of progestins will additionally help to minimize endometrial hyperplasia and prevent irregular bleeding (181). Rather than continue an estrogen and progestogen separately, a switch to the more convenient packaging in a low-dose estrogen-containing CHC then can be given to a cis-woman after breast development/vaginal breakthrough bleeding and peak bone mass are achieved with estrogen therapy alone, as in Turner syndrome (182, 183). For transwomen, a progestin is not needed long term and feminization cannot be achieved or sustained with CHCs (184, 185).

Contraception for pregnancy prevention in transgender individuals remains a poorly studied area. In transwomen, high-dose estrogen blocks spermatogenesis, though little is truly known about the effects of gender-affirming hormone therapy (GAHT) on the male reproductive system. A review by

Table 4. Example patient cases with suggested contraception selection and rationale

Case	Contraception suggestion	Rationale
18-year-old female with delayed puberty	Estrogen alone, followed by progesterone, and then a CHC	Estrogen to optimize breast development, progesterone for mammary ductule differentiation and minimization of endometrial hyperplasia. CHC for sex hormone maintenance/ contraception once puberty goals and peak bone mass achieved.
23-year-old female with PCOS or NCCAH	CHC with a less androgenic progestin ± anti-androgen (ie, spironolactone)	Suppress endogenous HPO-axis and increase SHBG to decrease androgens and reverse secondary amenorrhea in those not desiring fertility.
28-year-old female with hypogonadism	COCP with lower ethinyl estradiol dose or HRT with estrogen/progesterone	COCPs will lead to monthly withdrawal bleeds but HRT will provide estrogen supplementation to prevent poor long-term CV outcomes, bone, and fertility consequences of low estrogen status.
32-year-old female with recent DVT or PE	Nonhormonal contraception, progestin-only method, or CHC + anticoagulation	Estrogens will increase clotting risk, so a nonhormonal method or progestin-only method is indicated. CHCs can be used if anticoagulation is continued.
35-year-old with uncontrolled DM desiring pregnancy	Any effective contraceptive method A low-dose CHC is less likely to contribute to insulin resistance, and a CHC containing drospirenone may even improve insulin sensitivity.	A1c should be <6.5% before pregnancy in all women with T1 or T2 DM to optimize fetal and maternal outcomes. A low-dose CHC is less likely to contribute to insulin resistance, and a CHC containing drospirenone may even improve insulin sensitivity.
40-year-old woman with irregular menses	Levonorgestrel IUD or CHC containing lower dose ethinyl estradiol	Thin the uterine lining and regularize menses until menopause is achieved.

Example patient cases with suggested contraception selection based on patient profile with rationale for contraceptive method selected. These short cases are meant to be illustrative of how one might approach contraceptive selection for birth control and/or other desired endocrine outcomes. They are not meant to be complete representations of patients or their history. The authors recognize that there is a wide array of options in contraception selection and that practice patterns or preferences can differ significantly between patients and medical providers.
Abbreviations: A1c, hemoglobin A1c; CHC, combined hormonal contraceptive; COCP, combined oral contraceptive pill; CV, cardiovascular; DM, diabetes mellitus; DVT, deep vein thrombus; HPO, hypothalamic-pituitary-ovarian; HRT, hormone replacement therapy; IUD, intrauterine device; NCCAH, nonclassic congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome; PE, pulmonary embolus; T1, type 1; T2, type 2.

Mancini et al pointed out that studies assessing testis morphology were variable, with some showing the expected decrease in spermatogenesis, whereas a few demonstrated nearly normal testicular function. While transwomen are typically counseled on the high potential of decreased fertility once GAHT is started, those not desirous of fertility can opt for vasectomy (186). For transmen, the high doses of injectable testosterone used in GAHT is sufficient to block the HPG axis and ovarian function to lead to amenorrhea. However, amenorrhea does not equate to anovulation. Breakthrough ovulation may occur as FSH and LH do not return to prepubertal levels (186). Even if amenorrhea is achieved through testosterone, it is not considered contraception and necessitates contraceptive counseling as well as administration of contraception (187). The benefit of CHCs beyond contraception in transmen is to aid in suppressing menses. While continuous delivery of a transdermal patch, vaginal ring, or COCP will help with cessation of menses, use of a levonorgestrel-IUD might be preferred to potentially aid in the development of male secondary sex characteristics. In either case, the addition of a GnRH analogue as discussed previously could provide additional contraceptive benefit by suppressing pituitary release of LH and FSH.

Secondary Amenorrhea

The use of contraception in secondary amenorrhea where structural causes have been ruled out is straightforward as hormonal contraception will help to reestablish menses and/ or maintain a thin endometrial lining. In women with hypothalamic amenorrhea—a condition of severe hypoestrogenemia usually due to psychological stress, intense exercise, or disordered eating—the use of hormonal contraception is slightly more nuanced (188). Most women with hypothalamic amenorrhea require estrogen replacement to prevent the long-term cardiovascular, bone, and fertility consequences of prolonged low estrogen status. Low-dose estrogen and progestins have been recommended for bone protection (189). CHCs may provide some estrogen supplementation and will lead to a monthly withdrawal bleed but may not be sufficient to mimic normal endogenous estrogen function (188). The Endocrine Society guidelines recommended low-dose estradiol combined with cyclic progestin in adolescents due to their potentially more favorable effects on bone accrual (183, 189). However, this regimen does not provide contraception, and the underlying variability in the defect causing the hypothalamic amenorrhea can lead to irregular bleeding on such a regimen. Importantly, CHCs do not treat the underlying defect causing hypothalamic amenorrhea (190). Thus, CHCs may be used instead of estradiol and cyclic progestin since the severity of the defect varies over time.

Hyperandrogenism

For women with conditions predisposing them to hyperandrogenism—such as PCOS, congenital adrenal hyperplasia (CAH), and nonclassic CAH—or even those with familial or idiopathic hirsutism and acne, one could consider a trial of CHC or other hormonal contraceptive methods with an antiandrogenic progestin (191). In PCOS, CHCs are standard of care, with the additional benefit of improved quality of life (192, 193). However, women with PCOS display resistance to hypothalamic-pituitary-ovarian axis suppression with higher androgen levels on CHCs than non-PCOS women while on CHCs (194). Many clinicians tend to avoid oral

contraception or IUDs containing levonorgestrel in their patients with hyperandrogenism or switch if a patient has worsening symptoms.

In the dermatology literature, there are no head-to-head trials of different CHC formulations for hirsutism management, as EE will upregulate SHBG production regardless of whichever progestin it is paired with. How much the androgenicity of the progestin plays a role is debated as hypothalamic-pituitary-ovarian suppression and endogenous androgen release from ovarian theca cells is an important mechanism of action (195). However, progestins themselves have differential binding affinity to SHBG and may displace androgens (eg, endogenous testosterone, dihydrotestosterone), thereby reducing the antiandrogenic effects. Ultimately, progestins with the lowest SHBG-binding affinity (ie, norgestimate, drospirenone) may be a better choice or combining a CHC and spironolactone are also recommended (75, 150). Importantly, the CHCs approved to treat hirsutism were studied against placebo or levonorgestrel containing CHCs and not any other CHC options. A recent meta-analysis suggested COCPs with cyproterone acetate (which are not available in the United States and some European countries) may be better than other first- and second-generation COCPs, but recommended against its use because of VTE risk as well as risk of intracranial meningiomas at higher doses (191, 196). One would assume that the third- and fourth-generation CHCs might have better efficacy to control hyperandrogenic signs and symptoms; however, few studies have directly compared these outcomes.

In addition, the concern for a higher rate of VTE with drospirenone may concern the provider and patient (131). It is unclear if one can add spironolactone to CHCs containing drospirenone to increase effectiveness for treatment of hirsutism or acne without potential risks of hyperkalemia (197). Women with primary adrenal insufficiency might avoid CHC with drospirenone since it inhibits mineralocorticoids and mineralocorticoid replacement is the mainstay of primary adrenal insufficiency treatment (198). Some have suggested a regimen with a decreased number of placebo days in patients on CHCs to allow continuous suppression of androgens (199). Fewer placebo days have been associated with higher contraceptive efficacy for CHCs. For instance, 1 study highlighted that 24-day regimens have better efficacy compared to traditional 21-day regimens, while another demonstrated that even longer regimens, such as 84 days of active pills, result in lower pregnancy rates than 24-day ones (200, 201). From a clinical perspective, some providers may discuss the continuous use of CHCs with patients to potentially avoid biochemical rebound of androgens while maintaining the highest contraceptive efficacy. At least 1 randomized, double-blind trial (N = 62) demonstrated that continuous CHC use (168 consecutive days of active pills) resulted in greater ovarian and endometrial suppression as well as improved symptom control compared to a standard 21-day regimen given over 6 months, though at the cost of increased breakthrough bleeding (202). However, no controlled studies have been conducted to define the optimal window of placebo exposure to ensure endometrial shedding but not allow biochemical—and more importantly, clinical—rebound of hyperandrogenism.

When prescribing CHCs continuously in endocrine patients —such as in managing hyperandrogenic symptoms—some clinicians may have concerns about the long-term breast cancer risk associated with continuous progestogen (ie, a hormone with action at the progesterone receptor) exposure. This concern stems from data in postmenopausal women receiving progestogens as part of their hormone replacement therapy. These studies show an increased risk of breast cancer with continuous (vs intermittent) progestogen exposure, with greater risk observed with synthetic progestin compared to natural progesterone use (203-206). However, the relevance of these findings to premenopausal CHC users remains unclear. High-quality prospective studies, ideally with appropriate control groups, are needed to assess breast cancer risk across different CHC formulations, accounting for duration, adherence, and cumulative exposure. Until better data are available, medical providers are encouraged to individualize CHC counseling and weight potential long-term risks—especially for patients with elevated baseline breast cancer risk—against the known benefits of CHCs for managing endocrine symptoms (204, 207).

Diabetes

There were initial concerns with early hormonal contraception about CHCs altering glucose metabolism and the risk to women with diabetes, but this concern has been dispelled, especially with newer formulations (138). Though a 2019 study in rodents demonstrated that levonorgestrel-containing COCPs may affect glucose metabolism whereas drospirenone-containing COCPs do not increase the risk for diabetes (208, 209). Rather, the use of contraception to prevent an unplanned pregnancy in women with a hemoglobin A1c >6.5% is highly encouraged by major medical associations to decrease risks of adverse outcomes to a potential mother and her developing fetus (210-212). Though endocrinologists are uniquely poised to provide preconception counseling and contraception provision to reproductive-aged women with type 1 and type 2 diabetes mellitus, a recent quality improvement initiative done within an endocrinology practice at a tertiary hospital revealed that only 4% of women with diabetes had contraception documented by their endocrinologist (213). The majority of providers cited inadequate time during clinic visits to address contraception, though 32% stated that they lacked proper knowledge to provide this care. Current recommendations allow for any of the contraceptive choices to be available to those with diabetes understanding the risk/benefit of an unintended pregnancy (138). Concern is raised with diabetes duration more than 20 years with evidence of micro- or macrovascular disease. In those with uncontrolled hypertriglyceridemia, avoidance of oral estrogen is advised (133, 138). DMPA is avoided because of adverse effects on high-density lipoprotein cholesterol.

Overweight or Obesity

The surge in obesity rates alongside the explosion of newer antiobesity medications have elevated endocrinologists as primary prescribers of medical weight management therapies (214, 215). Use of contraception to prevent pregnancy during weight loss with medications is highly recommended, though injectable forms should be avoided (216, 217). While concerns about weight gain with contraceptive methods persist among patients, a review of 79 trials on CHCs revealed no significant difference in weight gain among combination contraception users (218). It is important to note that only 4 of these trials included a placebo or no-intervention group, and most strikingly, women with overweight or obesity were excluded from the analyzed studies. Similarly, another Cochrane review on

progestin-only contraceptives found minimal weight gain, yet the quality of evidence was poor given that 17 of the 22 included studies were nonrandomized trials (160). Despite the prevailing clinical consensus that most contraceptives do not cause weight gain, exceptions exist, notably DMPA, due to its potent action on glucocorticoid receptors (75). Moreover, recent research underscores contraceptives' broader impact on energy intake and energy expenditure on multiple biological levels (219). As such, prospective, controlled studies looking at the relationship between hormonal contraceptives and weight in those with a BMI ≥25 kg/m^2 are urgently needed.

Contraceptive efficacy in women with obesity is generally not of major concern as all hormonal methods work similarly in comparison to normal-weight counterparts. The 1 exception is with the contraceptive patch, which has a black box warning from the FDA of having reduced effectiveness in those with a BMI ≥30 kg/m^2 (130). VTE risk should instead be of greater concern for endocrinologists prescribing hormonal contraception to women with overweight or obesity. BMI is an independent risk factor for VTE, with women with obesity having a baseline increased risk that is 5 times that of their matched controls without obesity (137). When CHC is added, the VTE risk increases significantly but the absolute risk increase does depend on the formulation and route (137, 220). In general, with the exception of DMPA, progestin-only products are not associated with an increased risk of VTE (75). Women with obesity pursuing hormonal contraception should modify other risk factors to mitigate VTE risk, including controlling hypertension, quitting smoking, and increasing their physical activity.

Contraception Use in the Aging Female

We historically stopped CHCs at age 40 and limited their use >35 in women who smoke (221). In an otherwise healthy woman, CHCs can be continued until the time of menopause (222). However, comorbidities such as obesity, hypertension, hyperlipidemia, diabetes, or conditions would modify this option. In comparison, IUDs may be continued to menopause and beyond as some have suggested use of a levonorgestrel IUD with low-dose transdermal estrogen as a mode of postmenopausal hormone therapy to avoid oral progestin (223). Risk benefit of long-term administration is unknown.

Emerging Contraceptive Methods

Since the introduction of Enovid in the 1960s, the realm of contraceptive choices has undergone a remarkable expansion. This momentum persists with the emergence of increasingly innovative options that are either recently approved or currently in development. The following provides a brief overview of these advancements.

Female Contraceptive Methods

Given the obesity epidemic in the United States and increasing rates of comorbid conditions that preclude the use of classic estrogens found in contraception, there is an imperative need for novel estrogens. E4 has surfaced as an alternative estrogen that may alleviate some of the risks commonly found with estrogens in contraception (eg, EE, E2V) (105). Originally found in the fetal liver, E4 demonstrates estrogen receptor agonist properties in the endometrium and brain, thereby duplicating the HPG-suppressive properties of other estrogens. However, unlike other estrogens, E4 has antagonist properties in breast tissue, particularly in the presence of endogenous E2. Most importantly, E4 also appears to have differential effects in the hematological system and has been found to have far less influence on hematological factors associated with VTE when compared to other estrogens (224). E4 is theorized to potentially have less risk for VTE and other vascular diseases commonly associated with exogenous estrogen administration, but large-scale clinical data are lacking to support this theory. In the United States, E4 is only available in a single COCP formulation containing drospirenone 3 mg and estetrol 14.2 mg in a 24-4 monophasic formulation (Nextstellis, approved in 2021). In the pivotal clinical trials for Nextstellis, only 1 VTE event occurred in the 3632 participants from the trial conducted in Europe and Russia, whereas no VTE events occurred in the 2073 participants from the United States and Canada trial (225). Currently, this product still contains the FDA Black Box warning for increased risk of VTE, but future studies may demonstrate that this estrogen-containing product may be safe for use in certain patient populations that traditionally were not candidate for CHCs (226).

There is also an increasing demand for novel non-hormonal contraceptive methods for females, as patients and providers have become discontent with the lack of highly effective nonhormonal female contraceptive methods beyond the Cu-IUD. One such device still under clinical investigation is Ovaprene, which is a reuseable vaginal ring containing a mesh impregnated with ferrous gluconate and ascorbic acid (227). This device is inserted at the end the menses and kept in place until the following menses. While in place, the device prevents sperm from reaching the upper female genital tract through inhibiting motility. The pivotal postcoital test clinical trial with Ovaprene demonstrated that it reliably immobilizes sperm and should provide high contraceptive efficacy, which is now being investigated in a larger phase III clinical trial in the United States (228). As a nonhormonal reuseable device, this vaginal ring has the potential to expand the options for reliable contraceptive methods among individuals with contraindications or who experience adverse reactions to hormonal contraceptive methods.

Male Contraceptive Methods

In light of the increasing demand for more male contraceptive methods from both patients and health care providers, some progress has been made in developing hormonal contraceptive methods for males (229). Currently in phase II clinical trials, a transdermal gel that contains both a progestin (segesterone acetate) and testosterone has shown promise for inhibition of spermatogenesis through direct hypothalamic-pituitary-testosterone axis suppression while providing testosterone supplementation to reduce bothersome side effects (230). Designed as a daily gel, this product allows men to control their own contraception, but with the same drawbacks as all male hormonal contraceptive methods, a long lead-in time (up to 3 months or more) to achieve adequate sperm suppression to maintain contraceptive efficacy (230). Pending the results of the ongoing phase II clinical trial, this combined hormonal gel will still require a large phase III clinical trial before it can be approved by the FDA.

In addition to a transdermal gel, oral contraceptive pills containing dimethandrolone undecanoate or 11-beta-methyl-19–19-nortestosterone 17-beta-dodecylcardonate are both under investigation as potential male hormonal contraceptive methods. Both drugs have androgenic and progestogenic

properties, serving as potential single compound drugs for suppression of spermatogenesis without causing a hypoandrogenic state (230). Clinical studies with these 2 novel drugs are still in the early stages (preclinical or phase I) and so it remains to be proven if these will become safe and reliable male hormonal contraceptive methods.

Finally, many novel avenues of non-hormonal male contraception are being explored, including soluble adenylyl cyclase inhibitors, EPPIN inhibitors, immunocontraceptives, and many other small molecule targets. The goal for many of these new drug targets is to directly inhibit sperm motility or capacitation without affecting the HPG axis, thereby preventing sperm from reaching the ovum while avoiding the issues of lead-in time and hypoandrogenism that have plagued the development of male hormonal contraceptive methods. For a thorough review of nonhormonal male contraceptive development, we recommend the review published by O'Rand et al in *Pharmacology & Therapeutics* (231). A major obstacle for these nonhormonal contraceptive methods is proving safe and reliable reversibility, as historical pharmacologic products that acted as male contraceptive methods (eg, gossypol, triptolide) have suffered from unacceptable rates of irreversible sterility with simultaneous incomplete sterility, thus preventing these "natural" pharmacologics from moving forward as reversible contraceptive methods or sterilization options (232). Though promising targets have been identified for nonhormonal male contraception, the development of these drugs are still in preclinical stages with no product yet making it to phase I clinical trials in humans at the time of this review.

Multipurpose Prevention Technologies

Last, significant resources are being put into the development of multipurpose technologies that can serve as both contraceptive methods and infectious disease treatment or prevention. Vaginal rings have seen the most progress in this area, as they are a proven modality for female hormonal contraception while also providing a convenient avenue for administration of antiretrovirals for the prevention of HIV transmission. These multipurpose intravaginal rings typically contain a progestin already known to provide reliable female contraception in combination with an antiretroviral. One such multipurpose intravaginal ring contains levonorgestrel in combination with tenofovir and completed a phase I clinical trial in 2018 (233). Though multipurpose prevention technologies will largely be beyond the scope of practice for endocrinologists, they should still be aware of these potential devices as contraceptive methods that may be used by specific patient populations at high risk for transmissible infectious diseases.

Conclusion

Over the course of centuries, the progression from rudimentary contraceptive methods such as lint and animal-skin sheaths to modern innovations like the pill and nonoral birth control has been notable. This trajectory has led to a proliferation of contraceptive choices for women. While the responsibility for prescribing contraception for pregnancy prevention primarily lies outside the domain of endocrinologists, these specialists often utilize such interventions to manipulate sex hormone profiles for various therapeutic purposes. Although the direct prescription of multipurpose contraceptive technologies is unlikely to ever fall within the purview of endocrinologists, a significant shift in the contraceptive landscape is foreseeable with hormonal contraceptive pills becoming available over the counter, newer estrogens contained in CHCs, and the emergence of hormonal options tailored for male use. As testosterone-based contraceptive products gain FDA approval and become accessible to males, endocrinologists may find broader applications of these androgen-based methods beyond contraception within their practice. Nevertheless, it remains imperative for endocrinologists to possess comprehensive knowledge of the diverse contraceptive modalities available, along with their mechanisms of action, to adeptly leverage established mechanisms and clinical effects to achieve desired outcomes in the management of endocrine disorders.

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References

1. Guttmacher Institute. Contraceptive use in the United States [Internet]. 2024 May. https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states
2. United Nations Department of Economic and Social Affairs, Population Division. World Family Planning 2022: Meeting the Changing Needs for Family Planning: Contraceptive Use by Age and Method [Internet]. 2022 Dec. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2023/Feb/undesa_pd_2022_world-family-planning.pdf
3. Martinez GM, Daniels K. Fertility of men and women aged 15–49 in the United States: national survey of family growth 2015–2019. *Natl Health Stat Report* 2023;(179):1-22.
4. Skakkebaek NE, Lindahl-Jacobsen R, Levine H, *et al.* Environmental factors in declining human fertility. *Nat Rev Endocrinol*. 2022;18(3):139-157.
5. Vinicius L, Mace R, Migliano A. Variation in male reproductive longevity across traditional societies. *PLoS One*. 2014;9(11):e112236.
6. Nabhan AF, Mburu G, Elshafeey F, *et al.* Women's reproductive span: a systematic scoping review. *Hum Reprod Open*. 2022;2022(2):hoac005.
7. Anderson DJ, Johnston DS. A brief history and future prospects of contraception. *Science*. 2023;380(6641):154-158.
8. Lay J. A brief history of contraception [Internet]. In: *The Atlantic*. 2015. https://www.theatlantic.com/video/index/385602/a-brief-history-of-contraception/
9. Youssef H. The history of the condom. *J R Soc Med*. 1993;86(4):226-228.
10. Gilbirds WM 2nd, Jonas HS. The cervical cap. An alternate barrier contraceptive method. *Mo Med*. 1982;79(4):216-218, 224.
11. Drobner J, Fu MZ, Kaldany A, Velez-Leitner D. Historical review of the vasectomy: antiquated beliefs, novel techniques, and contemporary challenges. *Urology*. 2023;182:1-4.
12. Fanse S, Bao Q, Burgess DJ. Long-acting intrauterine systems: recent advances, current challenges, and future opportunities. *Adv Drug Deliv Rev*. 2022;191:114581.
13. Whittum M, Schickler R, Fanarjian N, Rapkin R, Nguyen BT. The history of female surgical sterilization. *J Gynecol Surg*. 2021;37(6):459-464.

14. Hanley GE, Pearce CL, Talhouk A, *et al*. Outcomes from opportunistic salpingectomy for ovarian cancer prevention. *JAMA Netw Open*. 2022;5(2):e2147343.
15. Oscar Hertwig (1849–1922). *Nature*. 1949;163(4146):596.
16. Junod SW, Marks L. Women's trials: the approval of the first oral contraceptive pill in the United States and Great Britain. *J Hist Med Allied Sci*. 2002;57(2):117-160.
17. Pérez A. General overview of natural family planning. *Genus*. 1998;54(3/4):75-93.
18. Latz L. *The Rhythm of Sterility and Fertility in Women*. Latz Foundation; 1939.
19. Valenza C. Was Margaret Sanger a racist? *Fam Plann Perspect*. 1985;17(1):44-46.
20. Goldzieher JW. Estrogens in oral contraceptives: historical perspectives. *Johns Hopkins Med J*. 1982;150(5):165-169.
21. Goldzieher JW. The history of steroidal contraceptive development: the estrogens. *Perspect Biol Med*. 1993;36(3):363-368.
22. Planned Parenthood Federation of America. The birth control pill: a history [Internet]. 2015 Jun. https://www.plannedparenthood.org/files/1514/3518/7100/Pill_History_FactSheet.pdf
23. Margulies L. History of intrauterine devices. *Bull N Y Acad Med*. 1975;51(5):662-667.
24. Watkins ES. The comeback of the IUD in twenty-first century USA. *J Hist Med Allied Sci*. 2021;76(2):191-216.
25. Roepke CL, Schaff EA. Long tail strings: impact of the Dalkon Shield 40 years later. *Open J Obstet Gynecol*. 2014;4(16):996-1005.
26. Sivin I, Greenslade F, Schmidt FH, Waldman SN. *The Copper T 380 Intrauterine Device: A Summary of Scientific Data*. Population Council; 1992.
27. Hohmann H, Creinin MD. The contraceptive implant. *Clin Obstet Gynecol*. 2007;50(4):907-917.
28. Gemzell-Danielsson K, Kubba A, Caetano C, Faustmann T, Lukkari-Lax E, Heikinheimo O. Thirty years of mirena: a story of innovation and change in women's healthcare. *Acta Obstet Gynecol Scand*. 2021;100(4):614-618.
29. Larsen SV, Mikkelsen AP, Ozenne B, Munk-Olsen T, Lidegaard Ø, Frokjaer VG. Association between intrauterine system hormone dosage and depression risk. *Am J Psychiatry*. 2024;181(9):834-841.
30. Elsayed M, Dardeer KT, Khehra N, *et al*. The potential association between psychiatric symptoms and the use of levonorgestrel intrauterine devices (LNG-IUDs): a systematic review. *World J Biol Psychiatry*. 2023;24(6):457-475.
31. Yi H, Zhang N, Huang J, *et al*. Association of levonorgestrel-releasing intrauterine device with gynecologic and breast cancers: a national cohort study in Sweden. *Am J Obstet Gynecol*. 2024;231(4):450.e1-450.e12.
32. Silva FR, Grande AJ, Macedo ACL, *et al*. Meta-analysis of breast cancer risk in levonorgestrel-releasing intrauterine system users. *Clin Breast Cancer*. 2021;21(6):497-508.
33. Natavio MF. Emergency contraception. In: Shoupe D, ed. *The Handbook of Contraception: Evidence Based Practice Recommendations and Rationales*. Springer International Publishing; 2020:183-192.
34. Lee JK, Schwarz EB. The safety of available and emerging options for emergency contraception. *Expert Opin Drug Saf*. 2017;16(10):1163-1171.
35. Practice Committee of American Society for Reproductive Medicine. Hormonal contraception: recent advances and controversies. *Fertil Steril*. 2008;90(5 Suppl):S103-S113.
36. Haddad LB, Townsend JW, Sitruk-Ware R. Contraceptive technologies: looking ahead to new approaches to increase options for family planning. *Clin Obstet Gynecol*. 2021;64(3):435.
37. Teal S, Edelman A. Contraception selection, effectiveness, and adverse effects: a review. *JAMA*. 2021;326(24):2507-2518.
38. Festin MPR. Overview of modern contraception. *Best Pract Res Clin Obstet Gynaecol*. 2020;66:4-14.
39. Genazzani AR, Fidecicchi T, Arduini D, Giannini A, Simoncini T. Hormonal and natural contraceptives: a review on efficacy and risks of different methods for an informed choice. *Gynecol Endocrinol*. 2023;39(1):2247093.
40. Altshuler AL, Blumenthal PD. Behavioral methods of contraception. In: Shoupe D, ed. *The Handbook of Contraception: Evidence Based Practice Recommendations and Rationales*. Springer International Publishing; 2020:239-254.
41. Hatcher R, Nelson A, Trussell J. *Contraceptive Technology*. 21st ed. Ayer Company Publishers, Inc; 2018.
42. Witt J, McEvers K, Kelly PJ. Knowledge and experiences of low-income patients with natural family planning. *J Nurse Pract*. 2013;9(2):99-104.
43. Yee LM, Simon MA. The role of health literacy and numeracy in contraceptive decision-making for urban Chicago women. *J Community Health*. 2014;39(2):394-399.
44. Frank-Herrmann P, Heil J, Gnoth C, *et al*. The effectiveness of a fertility awareness based method to avoid pregnancy in relation to a couple's sexual behaviour during the fertile time: a prospective longitudinal study. *Human Reproduction*. 2007;22(5):1310-1319.
45. Simmons RG, Jennings V. Fertility awareness-based methods of family planning. *Best Pract Res Clin Obstet Gynaecol*. 2020;66:68-82.
46. Prior J, Vigna Y, Schulzer M, Hall J, Bonen A. Determination of luteal phase length by quantitative basal temperature methods: validation against the midcycle LH peak. *Clin Invest Med*. 1990;13(3):123-131.
47. Earle S, Marston HR, Hadley R, Banks D. Use of menstruation and fertility app trackers: a scoping review of the evidence. *BMJ Sex Reprod Health*. 2021;47(2):90-101.
48. Goodale BM, Shilaih M, Falco L, Dammeier F, Hamvas G, Leeners B. Wearable sensors reveal menses-driven changes in physiology and enable prediction of the fertile window: observational study. *J Med Internet Res*. 2019;21(4):e13404.
49. Uchida Y, Izumizaki M. The use of wearable devices for predicting biphasic basal body temperature to estimate the date of ovulation in women. *J Therm Biol*. 2022;108:103290.
50. Lindh I, Othman J, Hansson M, Ekelund A-C, Svanberg T, Strandell A. New types of diaphragms and cervical caps versus older types of diaphragms and different gels for contraception: a systematic review. *BMJ Sex Reprod Health*. 2020;47(3):e12-e12.
51. Thomas MA, Chappell BT, Maximos B, Culwell KR, Dart C, Howard B. A novel vaginal pH regulator: results from the phase 3 AMPOWER contraception clinical trial. *Contracept X*. 2020;2:100031.
52. Guttmacher Institute. Contraceptive Effectiveness in the United States. Apr 2020. https://www.guttmacher.org/fact-sheet/contraceptive-effectiveness-united-states
53. Buhling KJ, Zite NB, Lotke P, Black K, Group IW. Worldwide use of intrauterine contraception: a review. *Contraception*. 2014;89(3):162-173.
54. Zini A, Grantmyre J, Chan P. CUA guideline: vasectomy. *Can Urol Assoc J*. 2016;10(7-8):E274-E278.
55. Marconi M, Weidner W. Site and risk factors of antisperm antibodies production in the male population. In: Krause W, Naz R, eds. *Immune Infertility: Impact of Immune Reactions on Human Fertility*. Springer International Publishing; 2017:133-147.
56. Dhruva SS, Ross JS, Gariepy AM. Revisiting essure--toward safe and effective sterilization. *N Engl J Med*. 2015;373(15):e17.
57. Fang NZ, Advaney SP, Castaño PM, Davis A, Westhoff CL. Female permanent contraception trends and updates. *Am J Obstet Gynecol*. 2022;226(6):773-780.
58. Tasset J, Jensen JT. Efficacy of tubal surgery for permanent contraception: considerations for the clinician. *Open Access J Contracept*. 2023;14:53-59.
59. Mills K, Marchand G, Sainz K, *et al*. Salpingectomy vs tubal ligation for sterilization: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2021;224(3):258-265.e4.

60. Kahn RM, Gordhandas S, Godwin K, *et al.* Salpingectomy for the primary prevention of ovarian cancer: a systematic review. *JAMA Surg*. 2023;158(11):1204-1211.
61. Date SV, Rokade J, Mule V, Dandapannavar S. Female sterilization failure: review over a decade and its clinicopathological correlation. *Int J Appl Basic Med Res*. 2014;4(2):81-85.
62. Sastre J, Mínguez JÁ, Alcázar JL, Chiva L. Microsurgical anastomosis of the fallopian tubes after tubal ligation: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2023;291:168-177.
63. Khaw SC, Anderson RA, Lui M-W. Systematic review of pregnancy outcomes after fertility-preserving treatment of uterine fibroids. *Reprod Biomed Online*. 2020;40(3):429-444.
64. Ibiebele I, Nippita TA, Baber R, Torvaldsen S. A study of pregnancy after endometrial ablation using linked population data. *Acta Obstet Gynecol Scand*. 2021;100(2):286-293.
65. Heylen A, Verguts J, Vandermeulen L, Van den Bosch T. Pregnancy following ablation therapy: a literature review. *J Endometr Uterine Disord*. 2023;4:100046.
66. Ghanaati H, Sanaati M, Shakiba M, *et al.* Pregnancy and its outcomes in patients after uterine fibroid embolization: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol*. 2020;43(8):1122-1133.
67. Ortiz ME, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. *Contraception*. 2007;75(6):S16-S30.
68. Lohr PA, Lyus R, Prager S. Use of intrauterine devices in nulliparous women. *Contraception*. 2017;95(6):529-537.
69. Foran T, Butcher BE, Kovacs G, Bateson D, O'Connor V. Safety of insertion of the copper IUD and LNG-IUS in nulliparous women: a systematic review. *Eur J Contracept Reprod Health Care*. 2018;23(5):379-386.
70. Dericks-Tan J, Koch P, Taubert H. Synthesis and release of gonadotropins: effect of an oral contraceptive. *Obstet Gynecol*. 1983;62(6):687-690.
71. Endrikat J, Gerlinger C, Richard S, Rosenbaum P, Düsterberg B. Ovulation inhibition doses of progestins: a systematic review of the available literature and of marketed preparations worldwide. *Contraception*. 2011;84(6):549-557.
72. Royer PA, Jones KP. Progestins for contraception: modern delivery systems and novel formulations. *Clin Obstet Gynecol*. 2014;57(4):644-658.
73. Schindler AE. Pharmacology of progestogens. In: Carp HJ, ed. *Progestogens in Obstetrics and Gynecology*. Springer International Publishing; 2021:31-38
74. Liu S, Kciuk O, Frank M, Tyson N. Progestins of today and tomorrow. *Curr Opin Obstet Gynecol*. 2022;34(6):344-350.
75. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;8(Suppl 1):3-63.
76. Pletzer B, Winkler-Crepaz K, Hillerer KM. Progesterone and contraceptive progestin actions on the brain: a systematic review of animal studies and comparison to human neuroimaging studies. *Front Neuroendocrinol*. 2023;69:101060.
77. Creinin MD, Jensen JT. Oral contraceptive generations–time to stop using a marketing myth to define nomenclature. *Contraception*. 2020;102(3):143-144.
78. Bick AJ, Louw-du Toit R, Skosana SB, Africander D, Hapgood JP. Pharmacokinetics, metabolism and serum concentrations of progestins used in contraception. *Pharmacol Ther*. 2021;222:107789.
79. Marques P, Skorupskaite K, Rozario KS, Anderson RA, George JT. Physiology of GNRH and gonadotropin secretion. In: *Endotext*. 2022.
80. Montoya ER, Bos PA. How oral contraceptives impact social-emotional behavior and brain function. *Trends Cogn Sci*. 2017;21(2):125-136.
81. Lovett JL, Chima MA, Wexler JK, *et al.* Oral contraceptives cause evolutionarily novel increases in hormone exposure: a risk factor for breast cancer. *Evol Med Public Health*. 2017;2017(1):97-108.
82. Fleischman DS, Navarrete CD, Fessler DM. Oral contraceptives suppress ovarian hormone production. *Psychol Sci*. 2010;21(5):750-752; author reply 753.
83. Baerwald AR, Pierson RA. Ovarian follicular development during the use of oral contraception: a review. *J Obstet Gynaecol Can*. 2004;26(1):19-24.
84. ESHRE Capri Workshop Group. Ovarian and endometrial function during hormonal contraception. *Hum Reprod*. 2001;16(7):1527-1535.
85. Crowley WF Jr, Filicori M, Spratt DI, Santoro NF. The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. *Recent Prog Horm Res*. 1985;41:473-531.
86. Hofmann BM, Apter D, Bitzer J, *et al.* Comparative pharmacokinetic analysis of levonorgestrel-releasing intrauterine systems and levonorgestrel-containing contraceptives with oral or subdermal administration route. *Eur J Contracept Reprod Health Care*. 2020;25(6):417-426.
87. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review: II. Mode of action. *Contraception*. 1994;50(6):S13-S21.
88. Bastianelli C, Farris M, Bruni V, Rosato E, Brosens I, Benagiano G. Effects of progestin-only contraceptives on the endometrium. *Expert Rev Clin Pharmacol*. 2020;13(10):1103-1123.
89. Wollum A, Zuniga C, Blanchard K, Teal S. A commentary on progestin-only pills and the "three-hour window" guidelines: timing of ingestion and mechanisms of action. *Contraception*. 2023;122:109978.
90. Hubacher D, Lopez L, Steiner MJ, Dorflinger L. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons. *Contraception*. 2009;80(2):113-118.
91. Moolhuijsen LM, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. *J Clin Endocrinol Metab*. 2020;105(11):3361-3373.
92. Girum T, Wasie A. Return of fertility after discontinuation of contraception: a systematic review and meta-analysis. *Contracept Reprod Med*. 2018;3(1):9.
93. Pfizer. Depo-Provera CI (medroxyprogesterone acetate) injectable suspension, for intramuscular use [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020246s036lbl.pdf. Revised October 2010 [cited 2024 Feb 24].
94. Schwallie P, Assenzo J. The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: a review. *Contraception*. 1974;10(2):181-202.
95. Zitzmann M, Rohayem J, Raidt J, *et al.* Impact of various progestins with or without transdermal testosterone on gonadotropin levels for non-invasive hormonal male contraception: a randomized clinical trial. *Andrology*. 2017;5(3):516-526.
96. Grandi G, Del Savio MC, Lopes da Silva-Filho A, Facchinetti F. Estetrol (E4): the new estrogenic component of combined oral contraceptives. *Expert Rev Clin Pharmacol*. 2020;13(4):327-330.
97. Haverinen A, Luiro K, Kangasniemi MH, *et al.* Estradiol valerate vs ethinylestradiol in combined oral contraceptives: effects on the pituitary-ovarian axis. *J Clin Endocrinol Metab*. 2022;107(7):e3008-e3017.
98. Nees LK, Heublein S, Steinmacher S, *et al.* Endometrial hyperplasia as a risk factor of endometrial cancer. *Arch Gynecol Obstet*. 2022;306(2):407-421.
99. Voedisch AJ, Fok WK. Oestrogen component of COCs: have we finally found a replacement for ethinyl estradiol? *Curr Opin Obstet Gynecol*. 2021;33(6):433-439.
100. Mawet M, Gaspard U, Foidart J-M. Estetrol as estrogen in a combined oral contraceptive, from the first in-human study to the contraceptive efficacy. *Eur Gynecol Obstet*. 2021;3(1):3-21.

101. Jensen JT. Evaluation of a new estradiol oral contraceptive: estradiol valerate and dienogest. *Expert Opin Pharmacother*. 2010;11(7):1147-1157.
102. Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. *Rev Endocr Metab Disord*. 2011;12(2):63-75.
103. Akintomide H, Panicker S. Nomegestrol acetate/17-beta estradiol: a review of efficacy, safety, and patient acceptability. *Open Access J Contracept*. 2015;6:77-86.
104. Haverinen A, Kangasniemi M, Luiro K, Piltonen T, Heikinheimo O, Tapanainen JS. Ethinyl estradiol vs estradiol valerate in combined oral contraceptives—effect on glucose tolerance: a randomized, controlled clinical trial. *Contraception*. 2021;103(1):53-59.
105. Fruzzetti F, Fidecicchi T, Montt Guevara MM, Simoncini T. Estetrol: a new choice for contraception. *J Clin Med*. 2021;10(23):5625.
106. Stanczyk FZ, Winer SA, Foidart J-M, Archer DF. Comparison of estrogenic components used for hormonal contraception. *Contraception*. 2023;130:110310.
107. van den Heuvel MW, van Bragt AJM, Alnabawy AKM, Kaptein MCJ. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005;72(3):168-174.
108. Reddy P, Rao J. Reversible antifertility action of testosterone propionate in human males. *Contraception*. 1972;5(4):295-301.
109. Heckel NJ. Production of oligospermia in a man by the use of testosterone propionate. *Proc Soc Exp Biol Med*. 1939;40(4):658-659.
110. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab*. 2009;94(3):907-913.
111. Thirumalai A, Page ST. Male hormonal contraception. *Annu Rev Med*. 2020;71(1):17-31.
112. Seminara SB, Hayes FJ, Crowley WF Jr. Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. *Endocr Rev*. 1998;19(5):521-539.
113. Marshall JC, Kelch RP. Gonadotropin-releasing hormone: role of pulsatile secretion in the regulation of reproduction. *N Engl J Med*. 1986;315(23):1459-1468.
114. Wildt L, Hausler A, Marshall G, *et al*. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. *Endocrinology*. 1981;109(2):376-385.
115. Abbe CR, Page ST, Thirumalai A. Male contraception. *Yale J Biol Med*. 2020;93(4):603-613.
116. Kavanaugh ML, Pliskin E. Use of contraception among reproductive-aged women in the United States, 2014 and 2016. *F S Rep*. 2020;1(2):83-93.
117. Daniels K, Abma JC. *Current Contraceptive Status Among Women Aged 15–49: United States, 2017–2019. NCHS Data Brief*. National Center for Health Statistics; 2020:1-8.
118. United Nations Department of Economic and Social Affairs, Population Division. World Family Planning 2022: Meeting the Changing Needs for Family Planning: Contraceptive Use by Age and Method [Internet]. 2022. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2023/Feb/undesa_pd_2022_world-family-planning.pdf
119. Van Vliet HA, Grimes DA, Lopez LM, Schulz KF, Helmerhorst FM. Triphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2011;2011(11):CD003553.
120. Van Vliet HA, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2006;2006(3):CD002032.
121. Van Vliet HA, Raps M, Lopez LM, Helmerhorst FM. Quadriphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2011 Nov;2011(11):CD009038.
122. Barton BE, Erickson JA, Allred SI, *et al*. Reversible female contraceptives: historical, current, and future perspectives. *Biol Reprod*. 2024;110(1):14-32.
123. Sullivan H, Furniss H, Spona J, Elstein M. Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 μg) and ethinyl estradiol (15 μg) on ovarian activity. *Fertil Steril*. 1999;72(1):115-120.
124. Wright KP, Johnson JV. Evaluation of extended and continuous use oral contraceptives. *Ther Clin Risk Manag*. 2008;4(5):905-911.
125. Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database Syst Rev*. 2014;2014(7):CD004695.
126. Karlsson T, Johansson T, Höglund J, Ek WE, Johansson Å. Time-dependent effects of oral contraceptive use on breast, ovarian, and endometrial cancers. *Cancer Res*. 2021;81(4):1153-1162.
127. Marchbanks PA, McDonald JA, Wilson HG, *et al*. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346(26):2025-2032.
128. Bachrach LK. Hormonal contraception and bone health in adolescents. *Front Endocrinol (Lausanne)*. 2020;11:603.
129. Birkhaeuser M. Hormonal contraception and bone. In: Meriggiola MC, Gemzell-Danielsson K, eds. *Female and Male Contraception*. Springer International Publishing; 2021:361-397
130. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2013;2013(4):CD003552.
131. Farris M, Bastianelli C, Rosato E, Brosens I, Benagiano G. Pharmacodynamics of combined estrogen-progestin oral contraceptives: 2. effects on hemostasis. *Expert Rev Clin Pharmacol*. 2017;10(10):1129-1144.
132. World Health Organization. Medical Eligibility Criteria for Contraceptive Use [Internet]. 2015 Feb. https://www.who.int/publications/i/item/9789241549158
133. Curtis KM, Tepper NK, Jatlaoui TC, *et al*. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-3):1-104.
134. McNicholas C, Zhao Q, Secura G, Allsworth JE, Madden T, Peipert JF. Contraceptive failures in overweight and obese combined hormonal contraceptive users. *Obstet Gynecol*. 2013;121(3):585-592.
135. Corium International, Inc. Twirla (levonorgestrel/ethinyl estradiol transdermal system) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204017s000lbl.pdf. Revised February 2020 [cited 2024 Feb 24].
136. Dragoman MV, Simmons KB, Paulen ME, Curtis KM. Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review. *Contraception*. 2017;95(2):117-129.
137. Rosano GMC, Rodriguez-Martinez MA, Spoletini I, Regidor PA. Obesity and contraceptive use: impact on cardiovascular risk. *ESC Heart Fail*. 2022;9(6):3761-3767.
138. ACOG practice bulletin no. 206: use of hormonal contraception in women with coexisting medical conditions: correction. *Obstet Gynecol*. 2019;133(6):1288.
139. Cooper DB, Patel P. Oral Contraceptive Pills In: *StatPearls [Internet]*. StatPearls Publishing; 2024 Feb 29. https://pubmed.ncbi.nlm.nih.gov/28613632/
140. Grandi G, Del Savio MC, Facchinetti F. The paradigm of norgestimate: a third-generation testosterone-derivative progestin with a peripheral anti-androgenic activity and the lowest risk of venous thromboembolism. *Expert Rev Clin Pharmacol*. 2021;14(2):211-224.

141. Westhoff CL, Eisenberger A, Tang R, Cremers S, Grossman LV, Pike MC. Clotting factor changes during the first cycle of oral contraceptive use. *Contraception*. 2016;93(1):70-76.
142. Pasapera AM, Gutiérrez-Sagal R, Herrera JN, Galicia-Canales N, de la Mora GGA, Ulloa-Aguirre A. Norethisterone is bioconverted to oestrogenic compounds that activate both the oestrogen receptor α and oestrogen receptor β in vitro. *Eur J Pharmacol*. 2002;452(3):347-355.
143. Cockrum RH, Soo J, Ham SA, Cohen KS, Snow SG. Association of progestogens and venous thromboembolism among women of reproductive age. *Obstet Gynecol*. 2022;140(3):477-487.
144. Morimont L, Haguet H, Dogné J-M, Gaspard U, Douxfils J. Combined oral contraceptives and venous thromboembolism: review and perspective to mitigate the risk. *Front Endocrinol (Lausanne)*. 2021;12:769187.
145. Kraft MZ, Rojczyk P, Weiss T, *et al*. Symptoms of mental disorders and oral contraception use: a systematic review and meta-analysis. *Front Neuroendocrinol*. 2024;72:101111.
146. de Wit AE, de Vries YA, de Boer MK, *et al*. Efficacy of combined oral contraceptives for depressive symptoms and overall symptomatology in premenstrual syndrome: pairwise and network meta-analysis of randomized trials. *Am J Obstet Gynecol*. 2021;225(6):624-633.
147. Noachtar IA, Frokjaer VG, Pletzer B. Mental health symptoms in oral contraceptive users during short-term hormone withdrawal. *JAMA Netw Open*. 2023;6(9):e2335957.
148. Teede HJ, Tay CT, Laven JJE, *et al*. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2023;108(10):2447-2469.
149. Cinar N, Harmanci A, Demir B, Yildiz BO. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study. *Hum Reprod*. 2012;27(6):1840-1845.
150. Trivedi MK, Shinkai K, Murase JE. A review of hormone-based therapies to treat adult acne vulgaris in women. *Int J Womens Dermatol*. 2017;3(1):44-52.
151. Gnoth C, Frank-Herrmann P, Schmoll A, Godehardt E, Freundl G. Cycle characteristics after discontinuation of oral contraceptives. *Gynecol Endocrinol*. 2002;16(4):307-317.
152. Horton LG, Simmons KB, Curtis KM. Combined hormonal contraceptive use among obese women and risk for cardiovascular events: a systematic review. *Contraception*. 2016;94(6):590-604.
153. Curtis KM, Tepper NK, Jatlaoui TC, *et al*. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*. 2016;65(3):1-103.
154. Kaiser Family Foundation. Contraceptive Implants [Internet]. 2019. https://www.kff.org/womens-health-policy/fact-sheet/contraceptive-implants/
155. Cohen R, Sheeder J, Kane M, Teal SB. Factors associated with contraceptive method choice and initiation in adolescents and young women. *J Adolesc Health*. 2017;61(4):454-460.
156. Rocca ML, Palumbo AR, Visconti F, Di Carlo C. Safety and benefits of contraceptives implants: a systematic review. *Pharmaceuticals (Basel)*. 2021;14(6):548.
157. Hou MY, McNicholas C, Creinin MD. Combined oral contraceptive treatment for bleeding complaints with the etonogestrel contraceptive implant: a randomised controlled trial. *Eur J Contracept Reprod Health Care*. 2016;21(5):361-366.
158. Jain J, Jakimiuk AJ, Bode FR, Ross D, Kaunitz AM. Contraceptive efficacy and safety of DMPA-SC. *Contraception*. 2004;70(4):269-275.
159. Paul C, Skegg DC, Williams S. Depot medroxyprogesterone acetate. Patterns of use and reasons for discontinuation. *Contraception*. 1997;56(4):209-214.
160. Lopez LM, Ramesh S, Chen M, *et al*. Progestin-only contraceptives: effects on weight. *Cochrane Database Syst Rev*. 2016;2016(8):CD008815.
161. Rahman M, Berenson AB. Predictors of higher bone mineral density loss and use of depot medroxyprogesterone acetate. *Obstetrics & Gynecology*. 2010;115(1):35-40.
162. Ortho-McNeil Pharmaceutical, Inc. Ortho Micronor (norethindrone) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/016954s101lbl.pdf. Revised June 2008 [cited 2024 Feb 24].
163. Cox H. The pre-coital use of mini-dosage progestagens. *J Reprod Fertil Suppl*. 1968;6:167-172.
164. Duijkers IJM, Heger-Mahn D, Drouin D, Colli E, Skouby S. Maintenance of ovulation inhibition with a new progestogen-only pill containing drospirenone after scheduled 24-h delays in pill intake. *Contraception*. 2016;93(4):303-309.
165. Jin X, Perrella SL, Lai CT, Taylor NL, Geddes DT. Causes of low milk supply: the roles of oestrogens, progesterone, and related external factors. *Advances in Nutrition*. 2023;15(1):100129.
166. Jackson E, Curtis KM, Gaffield ME. Risk of venous thromboembolism during the postpartum period: a systematic review. *Obstetrics & Gynecology*. 2011;117(3):691-703.
167. World Health Organization. II. Using the Recommendations. In: *Medical Eligibility Criteria for Contraceptive Use*. 5th ed [Internet]. World Health Organization; 2015. https://www.ncbi.nlm.nih.gov/books/NBK321153/#ch2
168. Calhoun AH, Batur P. Combined hormonal contraceptives and migraine: an update on the evidence. *Cleve Clin J Med*. 2017;84(8):631-638.
169. Zuniga C, Blanchard K, Harper CC, Wollum A, Key K, Henderson JT. Effectiveness and efficacy rates of progestin-only pills: a comprehensive literature review. *Contraception*. 2023;119:109925.
170. Practice bulletin no. 152: emergency contraception. *Obstet Gynecol*. 2015;126(3):e1-e11.
171. Rudzinski P, Lopuszynska I, Pazik D, *et al*. Emergency contraception—a review. *Eur J Obstet Gynecol Reprod Biol*. 2023;291:213-218.
172. Thompson I, Sanders JN, Schwarz EB, Boraas C, Turok DK. Copper intrauterine device placement 6–14 days after unprotected sex. *Contraception*. 2019;100(3):219-221.
173. World Health Organization. *Emergency Contraception [Internet]*. World Health Organization; 2021 Nov 9. https://www.who.int/news-room/fact-sheets/detail/emergency-contraception
174. Henry S, Shirin S, Goshtasebi A, Prior JC. Prospective 1-year assessment of within-woman variability of follicular and luteal phase lengths in healthy women prescreened to have normal menstrual cycle and luteal phase lengths. *Hum Reprod*. 2024;39(11):2565-2574.
175. de Blok CJM, Klaver M, Wiepjes CM, *et al*. Breast development in transwomen after 1 year of cross-sex hormone therapy: results of a prospective multicenter study. *J Clin Endocrinol Metab*. 2018;103(2):532-538.
176. Hasegawa Y, Hasegawa T, Satoh M, *et al*. Pubertal induction in Turner syndrome without gonadal function: a possibility of earlier, lower-dose estrogen therapy. *Front Endocrinol (Lausanne)*. 2023;14:1051695.
177. Arrington-Sanders R, Connell NT, Coon D, *et al*. Assessing and addressing the risk of venous thromboembolism across the spectrum of gender affirming care: a review. *Endocr Pract*. 2023;29(4):272-278.
178. Getahun D, Nash R, Flanders WD, *et al*. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med*. 2018;169(4):205-213.
179. Ramos G, Mengai A, Daltro C, Cutrim P, Zlotnik E, Beck A. Systematic review: puberty suppression with GnRH analogues in adolescents with gender incongruity. *J Endocrinol Invest*. 2021;44(6):1151-1158.
180. Othman ER, Al-Hendy A, Mostafa R, Lambalk CB, Mijatovic V. Oral GnRH antagonists in combination with estradiol and norethindrone acetate for pain relief associated with endometriosis: a

review of evidence of a novel class of hormonal agents. *Int J Womens Health*. 2024;16:309-321.
181. Zolfaroli I, Tarín JJ, Cano A. The action of estrogens and progestogens in the young female breast. *Eur J Obstet Gynecol Reprod Biol*. 2018;230:204-207.
182. Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab*. 2007;92(1):10-25.
183. Goshtasebi A, Subotic Brajic T, Scholes D, Beres Lederer Goldberg T, Berenson A, Prior JC. Adolescent use of combined hormonal contraception and peak bone mineral density accrual: a meta-analysis of international prospective controlled studies. *Clin Endocrinol (Oxf)*. 2019;90(4):517-524.
184. Milionis C, Ilias I, Koukkou E. Progesterone in gender-affirming therapy of trans women. *World J Biol Chem*. 2022;13(3):66-71.
185. Wierckx K, Gooren L, T'Sjoen G. Clinical review: breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014;11(5):1240-1247.
186. Mancini I, Alvisi S, Gava G, Seracchioli R, Meriggiola MC. Contraception across transgender. *Int J Impot Res*. 2021;33(7):710-719.
187. Light A, Wang LF, Zeymo A, Gomez-Lobo V. Family planning and contraception use in transgender men. *Contraception*. 2018;98(4):266-269.
188. Shufelt CL, Torbati T, Dutra E. Hypothalamic amenorrhea and the long-term health consequences. *Semin Reprod Med*. 2017;35(3):256-262.
189. Gordon CM, Ackerman KE, Berga SL, *et al*. Functional hypothalamic amenorrhea: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(5):1413-1439.
190. Falsetti L, Gambera A, Barbetti L, Specchia C. Long-term follow-up of functional hypothalamic amenorrhea and prognostic factors. *J Clin Endocrinol Metab*. 2002;87(2):500-505.
191. Forslund M, Melin J, Alesi S, *et al*. Different kinds of oral contraceptive pills in polycystic ovary syndrome: a systematic review and meta-analysis. *Eur J Endocrinol*. 2023;189(1):S1-S16.
192. Dokras A, Sarwer DB, Allison KC, *et al*. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J Clin Endocrinol Metab*. 2016;101(8):2966-2974.
193. Teede HJ, Tay CT, Laven JJE, *et al*. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Eur J Endocrinol*. 2023;189(2):G43-G64.
194. Daniels TL, Berga SL. Resistance of gonadotropin releasing hormone drive to sex steroid-induced suppression in hyperandrogenic anovulation. *J Clin Endocrinol Metab*. 1997;82(12):4179-4183.
195. Franks S, Willis DS, Mason HD, Gilling-Smith CM-T. Comparative androgen production from theca cells of normal women and women with polycystic ovaries. In: *Polycystic Ovary Syndrome*. Springer; 1996:154-164.
196. Lee KS, Zhang JJ, Kirollos R, Santarius T, Nga VDW, Yeo TT. A systematic review and meta-analysis of the association between cyproterone acetate and intracranial meningiomas. *Sci Rep*. 2022;12(1):1942.
197. Bird ST, Pepe SR, Etminan M, Liu X, Brophy JM, Delaney JA. The association between drospirenone and hyperkalemia: a comparative-safety study. *BMC Clin Pharmacol*. 2011;11(1):23.
198. Bornstein SR, Allolio B, Arlt W, *et al*. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(2):364-389.
199. Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary—ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception*. 2006;74(2):100-103.
200. Dinger J, Do Minh T, Buttmann N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. Cohort comparing progestogen and regimen. *Obstet Gynecol*. 2011;117(1):33-40.
201. Howard B, Trussell J, Grubb E, Lage MJ. Comparison of pregnancy rates in users of extended and cyclic combined oral contraceptive (COC) regimens in the United States: a brief report. *Contraception*. 2014;89(1):25-27.
202. Legro RS, Pauli JG, Kunselman AR, *et al*. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93(2):420-429.
203. Chlebowski RT, Anderson GL, Aragaki AK, *et al*. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. *JAMA*. 2020;324(4):369-380.
204. Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V. Combined and progestagen-only hormonal contraceptives and breast cancer risk: a UK nested case-control study and meta-analysis. *PLoS Med*. 2023;20(3):e1004188.
205. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*. 2017;377(23):2228-2239.
206. Asi N, Mohammed K, Haydour Q, Gionfriddo M, Vargas O, Prokop L. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. *Syst Rev*. 2016;5(1):121.
207. ACOG practice bulletin no. 206: use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol*. 2019;133(2):e128-e150.
208. Adeyanju OA, Olatunji LA. Drospirenone-containing oral contraceptives do not affect glucose regulation and circulating corticosterone. *J Basic Clin Physiol Pharmacol*. 2019;30(5):20180184.
209. Brabaharan S, Veettil SK, Kaiser JE, *et al*. Association of hormonal contraceptive use with adverse health outcomes: an umbrella review of meta-analyses of randomized clinical trials and cohort studies. *JAMA Netw Open*. 2022;5(1):e2143730.
210. American Academy of Family Physicians. Preconception care (position paper) [Internet]. 2015 Dec. https://www.aafp.org/about/policies/all/preconception-care.html
211. American College of Obstetricians Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin no. 201: pregestational diabetes mellitus. *Obstet Gynecol*. 2018;132(6):e228-e248.
212. ElSayed NA, Aleppo G, Aroda VR, *et al*. 15. Management of diabetes in pregnancy: standards of care in diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S254-S266.
213. Abushamat LA, Sayres L, Jeffers R, Nielsen C, Barbour LA, Zaman A. Unmasking barriers in the delivery of preconception counseling and contraception provision for patients with type 1 or type 2 diabetes. *Clin Diabetes*. 2023;41(4):567-572.
214. Suissa K, Schneeweiss S, Kim DW, Patorno E. Prescribing trends and clinical characteristics of patients starting antiobesity drugs in the United States. *Diabetes Obes Metab*. 2021;23(7):1542-1551.
215. Thomas CE, Mauer EA, Shukla AP, Rathi S, Aronne LJ. Low adoption of weight loss medications: a comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT 2s. *Obesity*. 2016;24(9):1955-1961.
216. Apovian CM, Aronne LJ, Bessesen DH, *et al*. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362.
217. Bays HE, Fitch A, Christensen S, Burridge K, Tondt J. Anti-obesity medications and investigational agents: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. *Obes Pillars*. 2022;2:100018.
218. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. *Cochrane Database Syst Rev*. 2014;2014(1):CD003987.
219. Metz L, Isacco L, Redman LM. Effect of oral contraceptives on energy balance in women: a review of current knowledge and potential cellular mechanisms. *Metabolism*. 2022;126:154919.
220. Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org; Practice Committee of the American Society for Reproductive Medicine.

Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril*. 2017;107(1):43-51.
221. de Bastos M, Stegeman BH, Rosendaal FR, *et al.* Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev*. 2014;2014(3):CD010813.
222. Bird ST, Delaney JA, Etminan M, Brophy JM, Hartzema AG. Drospirenone and non-fatal venous thromboembolism: is there a risk difference by dosage of ethinyl-estradiol? *J Thromb Haemost*. 2013;11(6):1059-1068.
223. Clark K, Westberg SM. Benefits of levonorgestrel intrauterine device use vs. oral or transdermal progesterone for postmenopausal women using estrogen containing hormone therapy. *Innov Pharm*. 2019;10(3):10.24926/iip.v10i3.2002.
224. Coelingh Bennink HJ, Holinka CF, Diczfalusy E. Estetrol review: profile and potential clinical applications. *Climacteric*. 2008;11(Suppl 1):47-58.
225. Apter D, Zimmerman Y, Beekman L, *et al.* Estetrol combined with drospirenone: an oral contraceptive with high acceptability, user satisfaction, well-being and favourable body weight control. *Eur J Contracept Reprod Health Care*. 2017;22(4):260-267.
226. Mayne Pharma. Nexstellis (drospirenone/estetrol) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214154s000lbl.pdf. Revised April 2021 [cited 2024 Feb 24].
227. Del Priore G, Malanowska-Stega J, Shalaby SW, Richman S. A pilot safety and tolerability study of a nonhormonal vaginal contraceptive ring. *J Reprod Med*. 2009;54(11-12):685-690.
228. Daré Bioscience. Ovaprene pipeline [Internet]. Daré Bioscience, Inc.; 2023. https://darebioscience.com/pipeline/ovaprene/
229. Dorman E, Bishai D. Demand for male contraception. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12(5):605-613.
230. Page ST, Blithe D, Wang C. Hormonal male contraception: getting to market. *Front Endocrinol (Lausanne)*. 2022;13:891589.
231. O'Rand MG, Silva EJ, Hamil KG. Non-hormonal male contraception: a review and development of an Eppin based contraceptive. *Pharmacol Ther*. 2016;157:105-111.
232. Kogan P, Wald M. Male contraception: history and development. *Urol Clin North Am*. 2014;41(1):145-161.
233. Tolley EE, Zissette S, Taylor J, *et al.* Acceptability of a long-acting, multipurpose vaginal ring: findings from a phase I trial in the U.S. and Dominican Republic. *J Womens Health (Larchmt)*. 2022;31(9):1343-1352.