The state of hormonal contraception today: benefits and risks of hormonal contraceptives: progestin-only contraceptives

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The progestin component of hormonal contraceptives accounts for most of their contraceptive effects. Several dosage forms of progestin-only contraceptives have been developed, including pills, injectables, implants, and intrauterine devices. Emergency contraceptives may also contain progestin only and are indicated for prevention of pregnancy following unprotected intercourse or contraceptive failure. Each form has benefits, some specific to the form. An understanding of benefits and risks allows clinicians a wider choice when recommending effective hormonal contraception.

Key words: emergency contraception, etonogestrel, levonorgestrel, medroxyprogesterone acetate, norethindrone

Types and characteristics of progestin-only contraceptives

The progestin component of hormonal contraceptives induces changes in the estrogen-primed endometrium, alters cervical mucus, and, in some cases, inhibits ovulation. The introduction of newer progestin-only methods provides additional contraceptive choices and maximizes effectiveness.

Four types of progestin-only contraceptives are currently available in the United States:

- Progestin-only daily oral contraceptives.
- Injectable 3-month contraceptives (depot medroxyprogesterone acetate [DMPA]), administered subcutaneously or intramuscularly.
- Etonogestrel single-rod implant, which provides effective contraception for at least 3 years.
- Intrauterine contraceptive (IUC) containing levonorgestrel, effective for at least 5 years.

Emergency contraceptive pills (ECs) also contain progestin. Two forms of oral ECs are available in the United States. One form delivers a total of 1.5 mg levonorgestrel. The other form is a newly approved single pill containing 30 mg ulipristal acetate, a progesterone agonist/antagonist. The effectiveness of ECs appears to result primarily from the inhibition or delay of ovulation. The levonorgestrel formulation should be taken within 72 hours, whereas the ulipristal acetate formulation can be taken up to 120 hours (5 days) after unprotected intercourse or known or suspected contraceptive failure.

Progestin-only contraceptives have several effects. The injectables and implants suppress ovulation, as may progestin-only pills (POPs) in some cases. In addition, progestin-only methods suppress endometrial activity. Over time, this causes endometrial atrophy, further contributing to the contraceptive effect and reducing the amount of menstrual blood loss. Finally, progestin thickens cervical mucus and impairs sperm transport, contributing to its effectiveness.

Newer progestins, such as drospirenone and desogestrel, have been developed to minimize the androgenic side effects that were attributed to their predecessors.

Benefits of progestin-only contraception

Benefits of progestin-only contraceptives include effectiveness, safety, and improvements in menstrual symptoms. The long-lasting reversible contraceptive methods—implants and IUC—are among the most effective reversible contraceptives, thanks to their “forgettability”: they are independent of daily action or intervention at the time of coitus. Noncontraceptive health benefits of progestin-only contraception include improvement in such symptoms as dysmenorrhea, menorrhagia, premenstrual syndrome, and anemia.

Progestin-only oral contraceptives

In clinical studies, POPs were associated with 12-month pregnancy rates ranging from 1-13%. Typical-use failure rates are estimated at about 8-9% per year, with perfect-use failure rates at 0.3% per year. Because serum progestin levels can be undetectable as early as 24 hours after POP ingestion, there is concern that their failure rates may be higher than combined oral contraception (COC) due to need for stricter adherence. A recent Cochrane Review found that there was insufficient evidence to determine whether effectiveness of POPs differs from that of COC. POPs containing norethindrone are available in the United States, whereas levonorgestrel and desogestrel pills are available internationally. POPs are taken every day, with no placebo or pill-free interval and no change in pill formulation. This feature can help some women maintain a regular pill schedule. Use of POPs may improve menstrual symptoms. POPs have traditionally been recommended for breast-feeding women because they have no adverse effect on lactation, but may also be a good option for other women.

DMPA

DMPA inhibits the secretion of gonadotropins, prevents follicular maturation and ovulation, and thins the endometrium. With perfect use of DMPA, the pregnancy rate is about 0.3 per 100 women annually, while typical-use preg-
nancy rates are closer to 3 per 100 women per year. A benefit of DMPA is the potential for amenorrhea or decreased menstrual blood loss over time. A review of both DMPA and levonorgestrel subdermal implants found that about 50% of women became amenorrheic after 1 year. After 1 injection, >10% of women may experience diminished or no menses, which may be of particular interest to those who have heavy menstrual bleeding or anemia or find menses inconvenient. DMPA has noncontraceptive health benefits as well. It may reduce painful crises in women with sickle cell disease and has been reported to decrease seizure activity in women with epilepsy in some studies. DMPA has also been shown to improve endometriosis symptoms at least as well as leuprolide acetate. Furthermore, because of endometrial suppression with medroxyprogesterone acetate, DMPA has a protective effect against the development of endometrial cancer. There are no known interactions between DMPA and other drugs.

Progestin implant

The etonogestrel-containing implant is a long-acting, reversible contraceptive that suppresses ovulation, increases viscosity of the cervical mucus, and alters the endometrium. It has a very low failure (pregnancy) rate, with a Pearl index of 0.38 pregnancies per 100 women. Ovulation resumes within 3 weeks of removal in >90% of women. The etonogestrel implant is cost-effective, providing 3 years of reliable contraception with relatively low expenditure when cost is averaged over time.

The noncontraceptive benefits of the etonogestrel-containing implant include improvement in endometriosis symptoms, improvement in dysmenorrhea, and decreased bleeding in some women. A series of case studies showed that the implant relieved pelvic pain in women with severe pelvic endometriosis. A review of data from 11 clinical trials, including >900 women, found that bleeding patterns were improved in 75% of women, and 77% of women who had baseline dysmenorrhea experienced complete resolution of their symptoms.

Progestin intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS) provides highly effective contraception for 5 years, with a failure rate between 0-0.2 per 100 woman-years and a low ectopic pregnancy rate of 0.01% per year. About 80% of women who wished to become pregnant conceived within 12 months of removal. With the LNG-IUS, menstrual bleeding is decreased by 75%, which is attributed to the progestin-induced decidualization and suppression of the endometrium. Amenorrhea is observed by about 20% of women after 1 year of use, with more women becoming amenorrheic over time. In addition to improving menorrhagia, anemia, and dysmenorrhea, the LNG-IUS likely also protects against endometrial cancer because of its suppression of the endometrium, although further research is needed to confirm this.

Risks of progestin-only contraceptives

There are few serious risks associated with the use of progestin-only contraceptives. The World Health Organization (WHO) and the Centers for Disease Control and Prevention eligibility guidelines list conditions for which use of progestin-only contraception may represent unacceptable health risks (category 3 or 4 recommendations). Breast cancer. Severe, decompensated cirrhosis of the liver. Liver tumors. Acute or recurrent deep vein thrombosis, pulmonary embolism. Stroke. Unlike combination hormonal contraceptives, however, progestin-only methods may safely be used in women with a history of hepatitis or in those with a history of venous thrombosis. Women with certain medical conditions such as multiple cardiac risk factors, vascular disease, or lupus often can use progestin-only methods, although the WHO advises that such women should perhaps consider other progestin-only methods than DMPA, which cannot be discontinued once injected.

Contraceptive implant

There are a few risks associated specifically with contraceptive implants. Although fairly uncommon, clinicians may experience complications of insertion and removal: if the rod is inserted too deeply or incorrectly, it may be difficult to remove. In early US trials, the rate of removal complications was 2%. Another caution concerns drug interactions. Etonogestrel is metabolized in liver microsomes by the cytochrome P450 enzyme system, and other medications that are metabolized similarly, specifically antiinfective agents and anticonvulsants, can result in drug/drug interactions. These pharmacokinetic changes raise the concern that such interactions will decrease the efficacy of the implant. Use of the implant is not contraindicated in such cases, however, and drug interactions may be more of a concern with POPs.

LNG-IUS

Risks of IUC use can include uterine perforation or expulsion, which may be accompanied by uterine bleeding and/or pain. The risk of expulsion is about 2-10% in the first year. Women who have expelled an IUC may be at increased risk for expulsion of subsequently placed devices. Women who have uterine anomalies preventing proper placement or unexplained vaginal bleeding should not use LNG-IUS. Women with fibroids may use LNG-IUS as long as these fibroids do not distort the cavity and interfere with the cavity. Women with fibroids do not distort the cavity and interfere with insertion. Like other progestin-only contraceptives, the LNG-IUS lowers risks of pelvic infection to 0-2%, although insertion in the presence of active chlamydial or gonorrheal infection may increase the risk up to 5%.

Side effects of progestin-only contraceptives

Progestin-only oral contraceptives

Irregular bleeding can be a side effect of POPs, as with other progestin-only methods. Over time, consistent use may lead to amenorrhea, which for some women may represent a benefit. Approximately 40% of women report regular cycles with POPs. Pharmacokinetic evidence suggests that some POPs could be less effective than combined pills; serum
hormone levels may be undetectable 27 hours after the last pill was taken. It is therefore recommended that women take the pills at the same time every day. Recent data, however, suggest that effectiveness of oral contraceptives is about the same for combined hormone and progestin-only formulations. Because there are few types of POPs available and they are not commonly used, their availability may be more limited than are COCs, which, in turn, can increase costs for some women.

**DMPA**

The perceived side effects of DMPA are a frequent reason for discontinuation, and counseling should anticipate this. Menstrual irregularities can cause discontinuation during the first year of use. Both bleeding and spotting are frequent during the first 3 months of DMPA use but decrease with each subsequent injection. The incidence of unscheduled bleeding/spotting days is about 70% in the first year and diminishes to about 10% thereafter. About 50% of DMPA users experience amenorrhea by year 1 of use and about 70% after 2 years of use.

Some clinical studies have found lipid changes, specifically decreased levels of high-density lipoprotein cholesterol and/or increased levels of low-density lipoprotein cholesterol in women using DMPA. Women using DMPA may report weight gain. In a recent prospective study, two-thirds of adolescent women using DMPA gained >2 kg (4.4 lb), whereas another study reported that some adult DMPA users maintained their initial body mass index (BMI) over time. The amount of weight gain can increase with longer use. A study of >700 women found that, after 3 years, DMPA users who completed the study had more weight gain than did COC users and nonusers of hormonal contraception. A systematic review found that weight gain with DMPA was not associated with baseline weight or BMI in adults but that obese/overweight adolescents gained more weight than did nonusers or DMPA users who were not overweight. There are no data to suggest that DMPA is less effective in obese women. Based on the results of 1 prospective study, DMPA seems to provide efficacious contraception to women even in higher BMI categories.

In 2004, the Food and Drug Administration issued a “black box warning” concerning the potential for loss of bone mineral density (BMD) in young women using DMPA. This warning was precipitated by the interpretation of studies suggesting that women using DMPA had reduced BMD compared with nonusers. However, losses in BMD, both in adolescent and adult women, are largely reversed when DMPA is discontinued. Importantly, DMPA has not been linked to increased fracture risk. Concerns about future skeletal health should not prevent the consideration of DMPA as an effective contraceptive choice for adults or adolescents.

**Progestin implant**

The most frequently reported side effects of the implant include irregular bleeding patterns. Although many women do have less bleeding overall, the bleeding/spotting episodes can occur at unpredictable intervals. A data review found that the etonogestrel implant was associated with the following bleeding irregularities: amenorrhea (22%), infrequent bleeding (34%), and frequent or prolonged bleeding (24%). Only 11% of women discontinued because of bleeding irregularities. Bleeding patterns may actually improve over time for the majority of women.

Other side effects of the etonogestrel implant include headache, breast tenderness, mood effects, and dysmenorrhea; these often resolve with time. Weight gain, about 4 lb in 2 years according to product labeling, seems to parallel what might be expected in nonusers. Over 3 years of implant use, about 14% of women may be expected to discontinue the product because of such adverse events.

**LNG-IUS**

Side effects of LNG-IUS include irregular bleeding patterns, which tend to be more common early in use and diminish over time, and amenorrhea in about 20% after a year. Women may experience cramping after insertion, and systemic absorption of levonorgestrel may vary causing progestin sensitivity in some women.

For all progestin-only methods, including long-acting options, effective counseling on bleeding changes and anticipated side effects can improve user satisfaction and increase continuation.

**Summary**

Several types of progestin-only contraceptives are available in the United States and worldwide. Some of these methods are highly effective. Progestin-only contraceptives are safe for most women and may offer noncontraceptive health benefits. Counseling women about expected side effects can improve their overall satisfaction and increase continuation rates.

**REFERENCES**

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