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Changing US trends in contraceptive choices

ABSTRACT

Long-acting reversible contraceptives (ie, intrauterine devices and the etonogestrel subdermal implant) have become increasingly popular methods of contraception because of their convenience and safety profile. At the same time, the use of depot medroxyprogesterone acetate, one of the most prescribed contraceptives in the United States since its approval in 1992, is on the wane. The history and pros and cons of these contraceptive methods are reviewed.

KEY POINTS

Depot medroxyprogesterone acetate (DMPA) must be administered by intramuscular injection (at a clinic) or subcutaneously (by the user) every 12 to 14 weeks.

Disadvantages to using DMPA include abnormal bleeding, weight gain, bone mineral density reduction, possible increased susceptibility to sexually transmitted infections, and ovulation delay after stopping use.

DMPA use has one of the highest discontinuation rates among all users of contraceptives.

Intrauterine devices (IUDs) (copper and levonorgestrel) are safe to use for nulliparity, pelvic inflammatory disease, heavy bleeding, and contraindications for estrogen therapy.

Contraindications for levonorgestrel IUDs include history of breast cancer, untreated cervical cancer, Müllerian anomalies, and gestational trophoblastic disease.

Over the past few decades, trends in the choice of contraceptive method have changed due to convenience, individual patient lifestyle, and adverse-effect profiles. Counseling patients on their best options can improve adherence and improve rates of unintended pregnancy.

This article examines the changing trends and reviews appropriate use of depot medroxyprogesterone acetate (17-acetoxy 6-methyl progestin; DMPA) and long-acting, reversible contraceptives (LARCs).

■ DMPA: A LONG-ACTING, REVERSIBLE CONTRACEPTIVE

DMPA is a long-acting, reversible progestational contraceptive without any estrogenic or androgenic activity. Although approved by the US Food and Drug Administration (FDA) in 1959 as a treatment for endometrial and renal cancers, it is now primarily used for contraception because of its ability to inhibit follicular maturation and ovulation.

Cancer risk an early but disproved concern

Subsequent to FDA approval for cancer therapy, DMPA was found to be a highly effective contraceptive at a 150-mg dose injected at 3-month intervals.[1] However, the FDA denied approval as a contraceptive agent in 1969, 1978, and 1983 because of safety concerns, primarily increased risk of endometrial, breast, ovarian, and cervical cancers found in animal studies.[2,3] However, the World Health Organization (WHO) later concluded no associated increased risk of breast, ovarian, or cervical cancers, and actually found substantially reduced endometrial cancer incidence and mortality.[4] This led to approval of

DMPA as a contraceptive in 1992,[4–6] after which DMPA quickly gained acceptance as one of few highly effective contraceptives at the time with a low per-dose cost.

Subcutaneous route allows self-administration

In 2004, a subcutaneous form of DMPA was FDA-approved with a 30% lower dose (104 mg every 3 months), offering an improved pharmacokinetic profile while providing more stability and sustained absorption because of low solubility.[7] Although peak serum levels are lower, duration of action is the same as provided by the intramuscular injection.[8] Subcutaneous DMPA can be administered in the thigh or abdomen every 12 to 14 weeks and was initially designed for self-administration in developing countries where patients have limited access to healthcare.[9]

Noncontraceptive benefits

DMPA has been recommended for female patients with certain medical conditions or preferences for the following reasons.

Bleeding reduction. DMPA can improve mean uterine and fibroid volume for patients with heavy menstrual bleeding from leiomyoma.[10] In a study of female patients with diagnosed endometrial hyperplasia, DMPA was associated with regression in 92% of patients after 6 months of treatment.[5] It should be considered for patients with endometrial hyperplasia who have contraindications to surgery and want to preserve fertility.[11]

Cancer prevention. DMPA is an effective chemopreventive agent for women at high risk of developing endometrial cancer (eg, patients with Lynch syndrome).[6]

Pelvic pain reduction. DMPA has success rates similar to other medical therapies for endometriosis (eg, danazol, combination contraceptives, gonadotropin-releasing hormone analogues) in managing deep dyspareunia and nonmenstrual pelvic pain after 1 year of use.[12]

◼ DMPA DRAWBACKS

DMPA has substantial drawbacks that have contributed to a decline in use.[13] It has the highest discontinuation rates among all contraceptives with side effects being the most common reason for stopping therapy.[14] However, DMPA continues to be commonly used in sub-Saharan Africa.[15]

Adherence to therapy is another challenge for DMPA therapy as clinic visits are required 4 times a year for intramuscular injection. A Planned Parenthood study followed 5,178 female patients prescribed DMPA: 57% returned for the second injection, 36% for the third injection, and only 23% continued therapy for 1 year.[16] The mean 1-year discontinuation rate has been reported to be 40% to 75%.[17]

Subcutaneous DMPA is associated with more injection-site reactions such as skin dimpling from lipodystrophy, and it is more expensive than the intramuscular form.[18]

Changes in menstrual bleeding

Effects on menstrual bleeding are often cited as one reason patients discontinue using DMPA.[9] Initially, progestin-only hormonal regimens can result in abnormal menstrual bleeding patterns; DMPA commonly causes spotting, irregular bleeding, and prolonged bleeding.[4] With prolonged use, DMPA is associated with amenorrhea, which many patients consider to be a benefit.[4,19] Reported rates are 52% to 64% at 12 months, and 71% at 24 months.

Combined hormonal contraceptives or estrogen supplementation may be used to manage bleeding in the short-term, but currently no effective long-term treatment methods have been identified.[4] Decreasing the administration interval to 10 weeks can reduce irregular bleeding for patients who have bleeding close to their next scheduled injection time. Very heavy and bothersome bleeding patterns warrant additional evaluation.

Ovulation delay

The DMPA clearance rate is variable. In overweight or obese patients, DMPA may be detected for up to 9 months after a single injection.[20] Generally, ovulation resumes within 14 weeks of DMPA discontinuation, although it may take up to 18 months.[21] On average, an additional 5 to 8 months is required to conceive after DMPA use compared with nonhormonal methods of contraception.[20]

Bone mineral density reduction

In 2004, the FDA added a black-box warning to the DMPA label, cautioning that prolonged use could result in loss of bone mineral density (BMD). Patients were advised to use long-term DMPA therapy only if they were unable

Female patients should be offered a wide range of contraceptive options and specific methods to fit their lifestyles

to use other contraception.[22] Compared with IUD users, DMPA users have more BMD reductions after 12 months of use.[23]

Hypoestrogenism from DMPA administration increases bone resorption over bone formation, contributing to the drug's skeletal effects.[24] Bone turnover markers, eg, alkaline phosphatase, increase within 12 months of DMPA use, suggesting increased bone resorption. In addition, glucocorticoid activity of DMPA decreases the proliferation of osteoblasts, leading to reduced bone formation.[25]

BMD loss appears to be more substantial in the initial 2 years of use, followed by a less intense nonlinear loss over the following years.[23] In adolescent girls, BMD values return to normal after DMPA is discontinued, with no differences noted compared with nonhormone users.[26] Perimenopausal patients who are vulnerable to a declining BMD may experience statistically significant bone loss with DMPA, increasing risk for developing osteoporosis.[9] However, a large study supported the safety of DMPA for use for 2 years or less, with only a modestly elevated absolute fracture risk in users compared with nonusers (adjusted hazards ratio 1.15 [95% confidence interval 1.01–1.31]).[27]

Use of DMPA beyond 2 years should not be absolutely contraindicated, as bone loss and fracture risk can return to baseline within 2 to 3 years after DMPA is discontinued,[28] especially in female patients with intact ovarian function. Although controversial, this recommendation is supported by the WHO and American College of Obstetricians and Gynecologists, regardless of patient age.[29] They recommend that providers discuss the black-box warning with patients, balancing the risks of using DMPA against the known health and social consequences associated with unintended pregnancy, particularly among adolescents.[29]

History of fracture is also not an absolute contraindication for DMPA use, and BMD monitoring is not recommended for current or previous DMPA users. However, it may be prudent to recommend lifestyle modifications, such as increasing physical activity, a diet rich in calcium, and vitamin D supplements.

Risk of sexually transmitted infections

Evidence indicates that DMPA may increase susceptibility to chlamydia, gonorrhea, herpes simplex, and human immunodeficiency virus (HIV).[4] Possible contributing causes are mucosal barrier disruption, inflammation, decreased humoral and cellular immune responses, and changes in the vaginal microbiome.[30–33] Consequently, the WHO issued a caution that women using progestin-only injectable methods of contraception should be strongly advised to use barrier protection (ie, male or female condoms).[4]

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial, conducted in sub-Saharan Africa, found that DMPA increased HIV transmission risk by 23% to 29% compared with the levonorgestrel IUD.[34] The authors concluded that the differences were not substantial, and the WHO used the results of this study to relax medical eligibility criteria for DMPA use in female patients at high risk for HIV infection. However, the study had a number of limitations, including lack of a control group of nonusers, casting doubt about the value of the results.[35] Further study is needed to provide clarity regarding HIV association.

Weight gain

Weight gain is a common concern for female patients starting contraceptive therapy. Most experts believe that DMPA use is more likely than other progestin contraceptives to lead to weight gain because of higher hormone levels and glucocorticoid activity.

Berenson et al[36] found that 36 months of DMPA use was associated with an average increase in body weight of 5.1 kg and an increase in body fat, percent body fat, and central-to-peripheral fat ratio compared with use of a combined hormonal contraceptive or nonhormonal method. Another study found a mean weight change over 12 months of 2.2 kg for DMPA users vs 1.0 kg for levonorgestrel IUD users.[37] In an unadjusted linear-regression model, DMPA use was associated with more weight gain than with use of a copper IUD.[36]

■ RECOMMENDATIONS FOR USE

DMPA is especially recommended as a contraceptive method for female patients with the following medical conditions and situations:
- Contraindications for estrogen-containing combined hormonal contraceptives, eg, migraine with aura (US Department of Health and Human Services Medical Eli-

DMPA use has one of the highest discontinuation rates among all contraceptives

gibility Criteria for Contraceptive Use [US MEC] category 1, ie, no restrictions), thrombogenetic variants (US MEC category 2, ie, advantages of using the method generally outweigh risks), and tobacco use in patients over age 35 (US MEC category 1).[38]

- DMPA does not appreciably affect blood pressure or increase risk of venous thromboembolism.
- Epilepsy: DMPA is associated with fewer antiepileptic drug interactions than combined hormonal contraceptives.
- Sickle cell disease: DMPA reduces the number of sickle cell crises.[39]
- DMPA can be used by female patients who have difficulty adhering to daily oral contraceptive regimens or have concerns about using implantable LARCs.

■ IUDS: NONHORMONAL AND HORMONAL

About 4.4 million women have an IUD in the United States,[40] where it has been available since 1968 and has been credited with national declines in overall unintended and teenage pregnancies.

Initial IUD had unacceptable risks

IUDs were initially made in a variety of shapes from different materials, including plastic and copper.[41] In 1971, the Dalkon Shield gained popularity, with an estimated 2 million users. However, this device was associated with significant rates of pelvic inflammatory disease, about 7,900 IUD-related hospitalizations, and 5 deaths, which were related to the multifilament-braided design of the IUD strings. In 1974, the device was removed from the market, and the manufacturer was responsible for approximately $500 million in compensatory and punitive damages, ultimately leading the company to file for bankruptcy. These events created controversy and distrust among patients seeking IUD contraceptive options.

Copper IUDS, an improvement

Alternate forms of IUDs have since been developed, including a copper-bearing version that debuted in the United States in 1988 (TCu380A or Paragard; CooperSurgical; Trumbull, CT).[42,43] Copper ions disrupt sperm motility and viability, and also increase white blood cell and prostaglandin levels within the uterus to prevent fertilization.

Copper-bearing IUDs are associated with increased cramping and heavier bleeding than the levonorgestrel IUD, but they remain an option for patients wanting nonhormonal LARC (eg, breast cancer survivors).[42]

Copper-bearing IUDs are currently the only LARC option approved for emergency contraception and can be inserted up to 5 days after unprotected intercourse. Evidence is emerging that the levonorgestrel IUD may also be effective for this indication.[43]

Levonorgestrel IUDs increasingly popular

IUDs containing the progestin levonorgestrel first became available in 2001, with rates of use increasing from 1.8% in 2002 to 9.5% in 2012 ($P < .001$), primarily in parous female patients who wanted to space additional pregnancies or who did not intend future pregnancies.[44]

Four levonorgestrel IUD options are now available: Mirena (levonorgestrel 52 mg, Skyla (levonorgestrel 13.5 mg, Kyleena (levonorgestrel 19.5 mg, and Liletta (levonorgestrel 52 mg). These hormone-containing IUDs are FDA-approved for use from 3 to 7 years, depending on the product.

A trained professional must insert an IUD. Procedural and postprocedural risks include expulsion (5.8%) and uterine perforation (0.1%).[45,46]

Safe to use in many settings

As the risk for pelvic inflammatory disease with IUDs is extremely low, no prior screening for sexually transmitted infections is necessary for asymptomatic and low-risk patients. IUDs may be offered to patients diagnosed with pelvic inflammatory disease as a contraceptive method.[47,48] Removal of an IUD has no therapeutic benefit for patients being treated for pelvic inflammatory disease and is not recommended.

IUDs can be safely used in patients who are nulliparous (a practice supported by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics), have contraindications to estrogen therapy, want LARC without the need for regular medical visits, and have heavy menstrual bleeding.

Contraindications

Absolute contraindications for the levonorgestrel IUD include a history of breast cancer, Müllerian anomalies (involving an abnormal uter-

Adverse effects, changes in menstrual bleeding, and adherence are often cited as reasons for discontinuing DMPA

TABLE 1

Characteristics of commonly used contraceptive methods

Medical condition	DMPA	LNG-IUD	CHCs	Subdermal implant
Unintended pregnancy rates	≤ 1%[56]	< 1%	9%	< 1%
WHO effectiveness tier	2 (highly effective)[57]	1 (most effective)	2	1
Drug interactions	Minimal	Minimal	Several[58]	Minimal
Influence on blood pressure	Minimal	Minimal	Can cause mild increase	Minimal[59]
Venous thromboembolism	Minimal	Minimal	Slight increase in risk[57]	Minimal[60]
Weight gain	Yes[36]	Minimal	Minimal	Minimal[59,61]
Influence on bone density	Negative[23]	Minimal	Positive[62]	Minimal[63]
Endometrium	Antiproliferative[4,6]	Antiproliferative[50]	Antiproliferative[64]	Antiproliferative[65]

CHCs = combined hormonal contraceptives; DMPA = depot medroxyprogesterone; LNG-IUD = levonorgestrel-releasing intrauterine device;
WHO = World Health Organization

Based on information in references 4, 6, 23, 36, 50, and 56–65.

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ine cavity shape), untreated cervical cancer, and gestational trophoblastic disease with persistently elevated beta-human chorionic gonadotropin.[49]

The US MEC recommend against levonorgestrel IUDs in patients with endometrial cancer. However, recent evidence suggests that levonorgestrel IUDs can be used to treat patients with early-stage, low-risk endometrial cancer who want to preserve fertility or who are not good candidates for surgery.[50]

Adverse effects

The primary adverse effect of the 52-mg levonorgestrel IUD is unscheduled bleeding that may last up to 12 weeks after insertion; this should be discussed with patients during contraceptive counseling.[46]

Amenorrhea can also occur. A secondary analysis of the Contraceptive CHOICE Project found that it was reported by 4.9% of 1,802 52-mg levonorgestrel IUD users at 3 months, 14.8% at 6 months, and 15.4% at 12 months.[51]

Other levonorgestrel IUD dosages may have slightly different bleeding profiles.

Several studies have found that body fat mass and weight can increase with use of the levonorgestrel IUD. However, gains after 12 months of use were not significantly different from gains in copper IUD users in one study.[52]

◼ SUBDERMAL ETONOGESTREL IMPLANT

The subdermal etonogestrel implant is another effective progestin-only LARC contraceptive option.[53] Inserted into the arm in an office procedure, it contains a single, radiopaque, extended-release rod that contains 68 mg of etonogestrel (a metabolite of desogestrel) and lasts for 3 years.[53]

The most common adverse effects are irregular bleeding, headache, and implant-site hematoma.[53] No changes in BMD or substantial weight gain were reported after 12 months of use.[54] Rates of discontinuation at 12 months for the subdermal implant are higher than for the levonorgestrel IUD or copper IUD, mostly due to menstrual cycle abnormalities.[55]

Comparisons of commonly used contraceptive methods are summarized in (**Table 1**).[4,6,23,36,50,56–65] More detailed recommendations can be found at websites for the US Centers for Disease Control and Prevention[66] and the US Medical Eligibility Criteria for Contraceptive Use.[67] ◼

◼ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

The DMPA label contains a black-box warning, cautioning that prolonged use may result in loss of bone mineral density

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