



Commentary

Society of Family Planning clinical recommendation: Extended use of long-acting reversible contraception☆☆☆

Divya Dethier^{a,*}, Neena Qasba^b, Bliss Kaneshiro^a^a Department of Obstetrics, Gynecology, and Women's Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, United States^b Department of Obstetrics and Gynecology, University of Massachusetts Chan Medical School – Baystate, Springfield, MA, United States

ARTICLE INFO

Article history:

Received 26 April 2022

Received in revised form 6 June 2022

Accepted 8 June 2022

Keywords:

Contraception

LARC

IUD

Implant

ABSTRACT

In this clinical recommendation, we review the evidence supporting the use of the copper intrauterine device, levonorgestrel intrauterine devices and etonogestrel subdermal implant beyond the Food and Drug Administration approved duration of use for contraception (extended use). Clinicians should discuss effectiveness as well as other clinical considerations with patients to allow them to make contraceptive decisions that support their reproductive goals and clinical needs. Extended use of long acting reversible contraception may be a safe, effective and desirable option for many patients.

© 2022 Elsevier Inc. All rights reserved.

1. Background

Long-acting reversible contraception (LARC), including intrauterine devices (IUDs) and the etonogestrel implant, are some of the most effective methods of contraception. As of 2022, 5 LARC devices are available in the United States: levonorgestrel 52 mg IUD (Mirena approved by the Food and Drug Administration [FDA] for 7 years, and Liletta FDA approved for 6 years), levonorgestrel 19.5 mg IUD (Kyleena FDA approved for 5 years), levonorgestrel 13.5 mg IUD (Skyla FDA approved for 3 years), copper 380 mm² IUD (Paragard FDA approved for 10 years), and etonogestrel 68 mg subdermal implant (Nexplanon FDA approved for 3 years). The levonorgestrel 52 mg IUD is the only LARC method that is also FDA-approved for the treatment of heavy menstrual bleeding, approved for 5 years for this indication. Evidence also supports the benefits of the etonogestrel 68 mg implant for the treatment of en-

dometriosis and adenomyosis, though it is not FDA-approved for this indication [1,2].

There are many advantages to extending LARC use for contraceptive and noncontraceptive benefits. Offering extended use of LARC in the setting of balanced counseling promotes patient centered care. Some patients may experience barriers to accessing family planning services (cost, lapses in insurance coverage, desire to reduce in-person office visits) or may have medical comorbidities that make removal and replacement challenging [3]. Others may simply want to continue using a device that continues to be effective at pregnancy prevention. Extended use of LARC can have individual and public health benefits [4]. Several methods (such as the Mirena and Liletta levonorgestrel 52 mg IUDs) have already been extended beyond their original FDA approval time frames, demonstrating that extended use is already a proven concept for LARC. Several studies, reviewed below, support continued contraceptive efficacy for LARC devices beyond the current FDA approved duration of use.

2. Clinical questions

2.1. What is the evidence regarding efficacy of the levonorgestrel 52 mg IUD beyond the FDA-approved window?

In August 2021, the FDA extended approval of the Mirena for pregnancy prevention from 6 to 7 years. Though Liletta is currently approved for 6 years, it adheres to similar manufacturing specifications producing a device that is identical in size, shape, and levonorgestrel dose. When Liletta was undergoing FDA approval, the

* Conflicts of interest: The authors have no conflicts of interest to report. Neena Qasba is a Merck Nexplanon Trainer and consultant to CooperSurgical. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries for the development of clinical guidance.

☆☆ A note on gender-inclusive language: we recognize that this guideline will apply to persons of all genders who were female sex-assigned at birth, who are using long-acting reversible contraception. We strive to use gender-inclusive language throughout this publication. However, when referencing research studies, we use the gender terminology reported by the study investigators, which is often "women."

* Corresponding author.

E-mail address: divyad@hawaii.edu (D. Dethier).

initial trial design included the Mirena as a comparator for European regulatory filing of Liletta; however, the Mirena arm was stopped after 159 subjects had been enrolled because it was determined that available contraceptive safety data from Mirena was sufficient to evaluate Liletta [5]. As such, we feel it is safe to consider Mirena and Liletta equivalent levonorgestrel 52 mg IUDs for the purpose of this Clinical Recommendation.

Bahamondes et al. [6] published a retrospective chart review of patients who continued the levonorgestrel 52 mg IUD beyond 60 months to a maximum of 15 years from placement. One hundred sixty women used the levonorgestrel 52 mg IUD beyond 7 years, resulting in a cumulative 1403 women-years of exposure up to 15 years with no pregnancies reported. Of the 160 women, 96 used it for 8 to 9 years, 31 used it for 10 to 11 years, 17 used it for 12 to 13 years, and 16 used it for 14 to 15 years. Most women had ongoing, increasing rates of amenorrhea after 7 years of use, suggesting an ongoing effect of levonorgestrel (75% of the 16 women who used the levonorgestrel 52 mg IUD past 13 years were amenorrheic). Reduced fecundity may have contributed to the low pregnancy rate; the mean age of placement was 32 years, with one-third under 30 years of age. The authors speculated that the release of levonorgestrel decreases beyond 7 years, but the plastic IUD provides ongoing contraception.

A phase 3 randomized open label multicenter trial looking at expanding use of the levonorgestrel 52 mg IUD (using Liletta) up to 10 years of use is ongoing. Preliminary data suggest high effectiveness and safety to 8 years of use. Four hundred seventy-eight patients have completed year 7, and 343 have completed year 8. Two pregnancies occurred in year 7 (1 ectopic, and 1 with implantation 4 days after IUD removal), and none in year 8. Amenorrhea rates were 39% at both years 7 and 8 [7].

After initial placement of any levonorgestrel IUD, an initial fast initial release of levonorgestrel is noted; after 60 days levonorgestrel release gradually declines over time. Pharmacokinetic studies of the levonorgestrel 52 mg IUD [8] reported mean levonorgestrel levels of 119 pg/mL at 102 months of use (8.5 years). Apter et al. compared the levonorgestrel 13.5, 19.5, and 52 mg IUDs and found that comparatively, the levonorgestrel 13.5 mg IUD resulted in serum levels of 58.6 pg/mL after 3 years of use [9]. Given that the serum level of the 52 mg IUD at 8.5 years is nearly twice that of the 13.5 mg IUD after 3 years, contraceptive efficacy of the levonorgestrel IUD past the FDA approved window of 7 years is likely. Extended use of the 52 mg levonorgestrel IUD beyond 8 to 10 years, may be offered cautiously and with careful counseling on risks and benefits, as the data currently available for this time frame is limited.

Patients should be counseled that the contraceptive effectiveness of the levonorgestrel 52 mg IUD is maintained beyond the current FDA-approved duration of 7 to 8 years (GRADE 1B).

2.2. What is the evidence regarding efficacy of the levonorgestrel 19.5 and 13.5 mg IUDs beyond the FDA-approved window?

We did not identify any studies describing contraceptive effectiveness with extended use of the levonorgestrel 19.5 mg or 13.5 mg IUDs. Based on data from Bahamondes et al., lower doses of levonorgestrel and the plastic IUD continue to provide some contraceptive effect [6]. Inert, plastic IUDs like the Lippes loop, created a spermicidal foreign body reaction in the endometrium that resulted in a pregnancy rate of 1.9 per 100 woman-years [10]. However, the size and shape of the inert IUDs contribute to contraceptive efficacy, with larger devices providing higher contraceptive effectiveness than smaller IUDs [11]. For levonorgestrel T-shaped IUDs, the relative contribution of the plastic device and the levonorgestrel to contraceptive efficacy remains unknown.

Pharmacokinetic studies show that the levonorgestrel 13.5 mg IUD at 3 years of use and the 19.5 mg IUD at 5 years of use result in a lower systemic exposure to levonorgestrel and lower incidence of anovulation, but have similar progestin impact on the endometrium and cervical mucus compared with the levonorgestrel 52 mg IUD [9,12]. Given that all levonorgestrel IUDs have relatively stable and similar progestogenic effects on the cervical mucus over 3 years, the 13.5 mg and 19.5 mg IUDs may have progestogenic effects beyond their current FDA duration of use. However, since no studies describe pharmacokinetics or contraceptive efficacy beyond the current FDA approved windows of 3 years for the 13.5 mg levonorgestrel IUD or 5 years for the 19.5 mg levonorgestrel IUD, we cannot draw definitive conclusions on the extended use of these IUDs.

2.3. What is the evidence regarding efficacy of the copper 380 mm² IUD beyond the FDA-approved window?

Data support the use of the copper 380 mm²IUD to 12 years of use with high effectiveness [13,14], and 2 studies support its use for pregnancy prevention until menopause [13,15]. A UNDP/Population Fund/WHO study in 1997 led by Rowe et al. showed no pregnancies between 8 and 12 years of use of the copper 380 mm² IUD, with 356 women completing 12 years [16]. Bahamondes et al. prospectively followed 228 women over age 35 who were still using the copper 380 mm²IUD after 10 years [13]. Women were followed for up to 16 years of use; 142 women used the copper 380 mm² IUD to 12 years, 31 women used it to 14 years, and 8 women used it to 16 years with no pregnancies noted (366 woman-years of observation). Reduced fecundity that accompanied extended years of use is likely to have contributed to low pregnancy rates.

In his review, Sivin noted no pregnancies from 15 to 20 years postinsertion of the copper 380 mm² IUD in 70 woman-years of observation [15]. Sivin's data, combined with Bahamondes et al.'s data, shows that over the 20-year observation period, with more than 1100 woman-years of observation, the cumulative pregnancy rate was 14.0 per 1000, the same rate observed at the end of 5 years of use though only 1050 woman-years were described for years 11-15 and only 7 woman-years of observation were reported for years 16 to 20.

Though these studies found reassuring contraceptive efficacy for the copper IUD out to 20 years of use, the generalizability of these findings is limited due to the patient inclusion criteria. Bahamondes' study only recruited women who were 35 years of age or older by the time they had completed 10 years of use, and Rowe's study excluded nulliparous women, among other exclusion criteria.

Overall, data supports continued efficacy of the copper 380 mm² IUD for 2 additional years of use, and with some evidence to support continued efficacy up to 5 additional years of use. Thus, the copper 380mm² IUD may be used as a permanent, reversible form of contraception when inserted after age 30, allowing women to have reliable contraception until age 45. Data beyond 15 years of use are too sparse to draw conclusions on efficacy, though the limited data available does suggest ongoing efficacy beyond 15 years of use. For women who are in their 40s, naturally reduced fecundity rates combined with extended use of the copper 380 mm² IUD even beyond 15 years may provide reliable, effective contraception until menopause.

Patients should be counseled that the contraceptive effectiveness of the copper 380 mm²IUD is maintained beyond the current FDA-approved duration of 10 to 12 years (GRADE 1B).

For patients over age 30 at time of insertion of the copper 380 mm² IUD, extended use beyond 12 to 20 years or to menopause, can be considered as a form of permanent, reversible contraception (GRADE 1C).

2.4. What is the evidence regarding efficacy of the etonogestrel 68 mg implant beyond the FDA-approved window?

Two studies describe extended use of the etonogestrel 68 mg implant to 5 years, with both reporting 100% effectiveness at pregnancy prevention. Ali et al. conducted a randomized study in 7 countries comparing safety and efficacy of the single-rod etonogestrel 68 mg implant, 2-rod levonorgestrel 75 mg implant (already approved for 5 years and not currently available in the US), or copper 380 mm² IUD for 5 years [17]. Two hundred and four women assigned to the etonogestrel implant completed 5 years of use. The cumulative pregnancy rate over 5 years for the etonogestrel implant was 0.6 with all attributed pregnancies occurring in the first 3 years of use. No additional pregnancies were noted in years 4 and 5. In the extended period, heavy menstrual bleeding was the only side effect significantly different between etonogestrel and levonorgestrel implant users, but the absolute rate was low at 12%. Providers reported slightly difficult or difficult removal in 2% of etonogestrel implant users after 5 years. Limitations included a low number of patients with a body mass index (BMI) greater than 30 in the etonogestrel arm ($n = 25$).

A study done in the United States described extended use of the etonogestrel 68 mg implant, in which over 50% ($n = 151$) of study participants had a BMI over 30 [18]. Researchers followed 291 patients past 3 years of use; 102 women used it for at least 24 additional months. No pregnancies were noted in years 4 and 5, and no difference was noted in median serum etonogestrel levels across BMI groups ($n = 58$ for BMI < 25, $n = 55$ for BMI 25–30, and $n = 127$ for BMI ≥ 30) at 3 and 5 years.

Merck is currently conducting a multi-center, multi-country phase 3 clinical trial to prospectively evaluate safety and efficacy of extended use of the etonogestrel 68 mg implant up to 5 years, with a goal to potentially extend its FDA approved use to 5 years if the trial data is supportive.

Patients should be counseled that the contraceptive effectiveness of the etonogestrel 68 mg implant is maintained beyond the current FDA-approved duration of 3 to 5 years (GRADE 1A).

2.5. What is the evidence regarding efficacy of other LARC devices beyond the approved window?

Other types of IUDs and implants are used globally. Though we focus on devices approved for use in the United States, other copper IUDs with varying doses of copper are used for extended durations of time. We did not identify any new data on extended use of globally available LARC devices from what has been described previously [19].

2.6. What considerations should there be with extended LARC use in patients with BMI above 30?

LARC methods are overall safe and effective regardless of BMI [20]. Effectiveness with extended use has not been adequately described in people of different weights but no reduction in the effectiveness has been suggested with the levonorgestrel 52 mg IUD and copper 380 mm²IUD based on BMI. Given the mechanism of action of IUDs, we can definitively state that the extended use of IUDs is independent of BMI.

Xu et al. noted no variation in effectiveness by BMI for the standard 3-year duration of use with the etonogestrel 68 mg implant [21]. Mornar et al. examined the pharmacokinetics of the etonogestrel 68 mg implant in obese women from insertion to 6 months, enrolling 13 women with a median BMI of 41 (ranges 33–52) [22]. The plasma etonogestrel concentration-time curves were similar in shape to normal weight women, but the etonogestrel concentrations were consistently lower in the obese cohort, reaching an av-

erage steady state concentration of 227.9 pg/mL at 6 months. With 2 years of additional use, McNicholas et al. reported no additional pregnancies in year 3 or 4 of use regardless of BMI. Of the 151 participants with a BMI of 30 or higher, the proportion who met the criteria for class 1, 2, or 3 obesity categories was not reported [18]. A study by Lazorwitz et al. showed a statistically significant association between increasing BMI and lower serum etonogestrel concentrations [23]. Of note, Black/African American race was a positive effect modifier in this study population. However, the effect of BMI was not significant enough in the majority of patients to cause the etonogestrel concentration to drop below 90 pg/mL. The clinical cut off of 90 pg/mL is the etonogestrel concentration necessary to effectively prevent ovulation, but the minimum serum etonogestrel concentration needed to maintain contraceptive efficacy by other progestin effects is unknown. These data suggest a lower ENG concentration with higher BMI categories. More research is needed in this area, especially with BMI over 50. Given this data, we cannot definitely identify a BMI cut-off above which the ENG implant may have reduced effectiveness with extended use.

Patients should be counseled that the contraceptive effectiveness with extended use of IUDs is independent of BMI (GRADE 1B).

Extended use of the implant may be offered in patients of any BMI. However, given data is limited in patients with class 3 obesity and above (BMI > 40), shared decision making and careful weighing of risks and benefits is warranted (GRADE 2B).

2.7. Should age be considered when offering extended LARC use?

Fecundity and the risk of pregnancy decreases as age increases, though the possibility of pregnancy exists for all with reproductive potential until menopause. Several studies on extended use of the copper 380 mm² IUD report comparable, even lower rates of pregnancy as those observed with permanent sterilization, though surgical sterilization and the copper 380 mm² IUD have not been directly compared in a study [13,15].

Studies describing extended use of LARC in adolescents have not been published. The CHOICE study demonstrated effectiveness of LARC is not altered in adolescents and young women [24]. Method continuation and satisfaction are also higher with LARC than other methods among adolescents [25]. While specific evidence on extended use of LARC in adolescents does not exist, extended use can still be offered to adolescents as it would to adult patients in the context of shared decision-making.

Adolescents may be counseled regarding extended use of LARC (GRADE 1C).

2.8. How does extended LARC use affect bleeding patterns?

Extended use may be associated with changes in bleeding pattern. Amenorrhea in levonorgestrel 52 mg IUD users increases over time; the 1-year amenorrhea rate is approximately 18% and reaches 40% by years 5 and 6 [26,27]. Bahamondes et al. described even higher rates of amenorrhea in levonorgestrel 52 mg IUD users with extended use, with 55% reporting amenorrhea after 5 years of use and 62.5% after 7 years of use [6]. Few patients reported irregular or heavier bleeding after 5 years of use.

Limited studies suggest the copper 380 mm² IUD is not associated with significant bleeding pattern changes with extended use until the perimenopausal period. Bahamondes et al. reported that in year 15 or 16 of use, during the menopausal transition, participants in their study population reported irregular menstrual cycles, intermenstrual bleeding, and pain [13].

The amenorrhea rate during the first 2 years of use for the etonogestrel 68 mg implant is approximately 22% [28]. During years 4 and 5 of extended use, Ali et al. reported amenorrhea in

8% of users and heavy bleeding in 12% of users. Irregular bleeding was most commonly reported, accounting for 46% of users [17].

2.9. How does extended LARC use impact other medication interactions?

Patients should be counseled regarding the potential for decreased contraceptive effectiveness with typical and extended use of the etonogestrel 68 mg implant with concomitant administration of medications that are CYP3A4 inducers, such as rifampin and rifabutin, some antiretrovirals (ARVs) and antiepileptics. Though data are limited, several studies report reduced serum levels of etonogestrel with the contraceptive implant in patients using some enzyme inducing medications during the first 3 years of use. Robinson et al. reported a series of case reports of contraceptive failures in patients on efavirenz, a known inducer of hepatic P450 activity [29,30]. Resulting pregnancies occurred after 24 months of implant use, suggesting that early replacement may be warranted in patients using these medications.

Lazorwitz et al. noted 8 of 10 patients on carbamazepine had etonogestrel concentrations below the threshold for ovulatory suppression, though pharmacodynamic parameters (follicle development and endometrial thickness) did not change [31]. Leticee et al. reported a case of pregnancy after 25 months of implant use in a patient that was taking carbamazepine [32].

Lazorwitz et al. studied concomitant topiramate use in 48 etonogestrel implant users [33]. They found dose-dependent, inferior serum etonogestrel concentrations at levels below the threshold for ovulation suppression in patients using topiramate at antiepileptic dosages (>200 mg/d). However, the authors note that serum etonogestrel concentrations are a surrogate marker for risk of contraceptive failure, but the minimal serum etonogestrel concentration needed to maintain efficacy through secondary mechanisms, such as cervical mucous thickening or delayed sperm transport is not known.

Rifampin and rifabutin are anti-mycobacterial drugs that have strong CYP3A4 inducing activity and may affect metabolism of progestin that can impact contraceptive efficacy [34]. Several case reports describe contraceptive failures and unintended pregnancy in women with ENG implant that were taking rifampin/rifabutin [35,36].

The CDC MEC gives copper and levonorgestrel IUDs a category 1 for all enzyme-inducing drugs [20]. No published data exist to support that CYP3A4 inducing drugs affect the efficacy of levonorgestrel IUDs. ARVs did not affect contraceptive efficacy in levonorgestrel 52 mg IUD users [29]. No data exists on the effectiveness of lower dose levonorgestrel IUDs with concomitant ARV use; however, given levonorgestrel IUDs act locally and do not rely upon systemic progestin exposure for their primary contraceptive mechanism, we can theorize that ARVs also would not affect contraceptive efficacy in the lower dose levonorgestrel IUDs.

Effectiveness may be reduced with extended implant use in patients taking medications that are CYP3A4 inducers; use of shared decision making and careful weighing of risks and benefits in these situations is warranted (GRADE 2C).

Patients taking CYP3A4 inducing medications may be offered extended use of IUDs (GRADE 1C).

2.10. Does extended LARC use make device removal more challenging?

Limited data suggests that most patients who use LARC for an extended period of time will not experience a difficult removal. Implanted foreign bodies like the contraceptive implant may be subject to more inflammatory processes causing fibrous adhesions. Drawing from experience with the 6-rod levonorgestrel implant,

some clinicians cite concerns about difficult removal with extended use of the contraceptive implant. Ali et al. reported approximately 2% of etonogestrel implant users, which included 6% of patients with a BMI above 30, had slightly difficult or difficult removals at the end of the 5 years [17]. Chevreau et al. concluded that longer use (>25 months) was independently associated with difficult removal (RR 2.91) which was defined as having a previous failed removal attempt [37]. Ultrasound was performed prior to removal and found that 24% of the people in the difficult removal group had an implant placed below the sub-brachial fascia. Approximately 24% of the people in the difficult removal group had a BMI above 30, though this was not associated with an increased likelihood of difficult removal. Chevreau et al. did however find that weight gain of >1kg was associated with more difficult removal (RR 1.90). Extending use of the implant would provide a longer time span for patient weight fluctuations and thus potential risk of challenging device removal.

Limited data exists regarding difficult removal following extended use of the levonorgestrel or copper IUD. In Teal et al's study, of all patients who used the levonorgestrel 52 mg IUD up to or beyond 7 years, only 2 removals out of 1110 could not be completed in the office. The reason for difficult removal was not noted [26].

2.11. How do we center patient preference in counseling patients regarding extended LARC use?

Providers should discuss and review extended use of LARC devices with all patients. Counseling on extended LARC use should center around patient priorities and preferences. Discussions should include information on the risks of extended use, including waning effectiveness, bleeding changes, and removal, as well as the benefits of extended use, including avoiding another replacement procedure and maintaining continuous contraceptive coverage. Other patient considerations may include the cost of replacement procedures, timeliness of replacement visits and avoiding use of short-acting, less effective "bridge" methods, such as barrier methods or pill, patch, ring.

In certain situations, such as a global pandemic, national disasters, violence/war, or other type of public health crisis, health care facilities may minimize or temporarily stop nonurgent in-person visits. The benefits of extending use of their LARC method may outweigh the risk of an in-person visit and/or may be preferable to patients in these situations. Patient education on safe self-removal can also be discussed with patients [38]. Please see "SFP interim clinical recommendations: Contraceptive provision when health-care access is restricted due to pandemic response" for further information on contraception care during the coronavirus disease 2019 pandemic [39].

Patient autonomy and preference are important and valid reasons for offering extended LARC use (GRADE 1C).

3. Conclusions and recommendations

The following recommendations are based primarily on good quality scientific evidence:

- Patients should be counseled that the contraceptive effectiveness of the levonorgestrel 52 mg IUD is maintained beyond the current FDA-approved duration of 7 to 8 years (GRADE 1B).
- Patients should be counseled that the contraceptive effectiveness of the copper 380 mm² IUD is maintained beyond the current FDA-approved duration of 10 to 12 years (GRADE 1B).
- Patients should be counseled that the contraceptive effectiveness of the etonogestrel 68 mg implant is maintained beyond the current FDA-approved duration of 3 to 5 years (GRADE 1A).

- Patients should be counseled that the contraceptive effectiveness with extended use of IUDs and implants is independent of BMI (GRADE 1B).
- Patients should be counseled that the contraceptive effectiveness with extended use of IUDs is independent of BMI (GRADE 1B).
- Extended use of the implant may be offered in patients of any BMI. However, given data is limited in patients with class 3 obesity and above (BMI > .40), shared decision making and careful weighing of risks and benefits is warranted (GRADE 2B).

The following recommendations are based primarily on consensus and expert opinion:

- For patients over age 30 at time of insertion of the copper 380 mm² IUD, extended use beyond 12 to 20 years or to menopause, can be considered as a form of reversible, permanent contraception (GRADE 1C).
- Adolescents may be counseled regarding extended use of LARC (GRADE 1C).
- Effectiveness may be reduced with extended implant use in patients taking medications that are CYP3A4 inducers; use of shared decision making and careful weighing of risks and benefits in these situations is warranted (GRADE 2C).
- Patients taking CYP3A4 inducing medications may be offered extended use of IUDs (GRADE 1C).
- Patient autonomy and preference are important and valid reasons for offering extended LARC use (GRADE 1C).

4. Recommendations for future research

- Randomized trials or observational studies on extended duration of use of levonorgestrel 19.5 mg and 13.5 mg IUDs
- Pharmacokinetic studies on extended use of the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg IUDs
- Pharmacokinetic studies on the minimum etonogestrel concentration needed to maintain contraceptive efficacy through non-ovulatory suppression mechanisms
- Pharmacokinetic studies on the minimum levonorgestrel daily dose that provides contraceptive benefit beyond that provided from a T-shaped inert IUD
- Prospective studies on extending duration of use of etonogestrel 68 mg implant beyond 5 years
- Prospective studies on extended duration of the levonorgestrel 52 mg IUD in women over 35 as a form of reversible, permanent contraception
- Cost-benefit analyses of extended duration of use of LARC devices
- Cohort studies on efficacy of extended duration of use of LARC devices in patients with class 1, 2, and 3 obesity
- Cohort studies on efficacy of extended duration of use of LARC devices in patients under age 25
- Qualitative studies on patient experiences and preferences for extended duration of use LARC devices

Sources

A series of clinical questions was developed by the authors and reviewed by the Executive Board of the Society of Family Planning and Clinical Affairs subcommittee. A search of the medical literature was performed using the PubMed program of the National Library of Medicine, as well as ClinicalTrials.gov of the National Library of medicine, from the beginning of the databases through May 30, 2022. Search terms included, but were not limited to, extended use, LARC, levonorgestrel IUD, copper IUD, etonogestrel implant. For ongoing clinical trials, if no preliminary data was yet published, the principal investigators were contacted to

inquire about any existing preliminary data. A comprehensive systematic review was not performed.

Intended audience

Contraceptive care providers in ambulatory settings. This set of recommendations should guide clinicians in their medical decision-making. These recommendations should not dictate clinical care.

Authors' contributions

These recommendations were prepared by Divya Dethier, Neena Qasba, and Bliss Kaneshiro, and were reviewed and approved by the Clinical Affairs Committee on behalf of the Board of Directors of the Society of Family Planning.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Carvalho N, Margatho D, Cursino K, Benetti-Pinto CL, Bahamondes L. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. *Fertility and Sterility* 2018;110:1129–36. doi:10.1016/j.fertnstert.2018.07.003.
- [2] Niu X, Luo Q, Wang C, Zhu L, Huang L. Effects of Etonogestrel implants on pelvic pain and menstrual flow in women suffering from adenomyosis or endometriosis: Results from a prospective, observational study. *Medicine* 2021;100:e24597. doi:10.1097/MD.00000000000024597.
- [3] ACOG Practice Bulletin 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstetrics and Gynecology* 2017;130(5).
- [4] Zapata LB, Curtis KM, Steiner RJ, Reeves JA, Nguyen AT, Miele K, et al. COVID-19 and family planning service delivery: Findings from a survey of U.S. physicians. *Preventive Medicine* 2021;150:106664. doi:10.1016/j.ypmed.2021.106664.
- [5] Food and Drug Administration. Clinical review: Liletta levonorgestrel (LNG)-releasing intrauterine system (IUS). 2019.
- [6] Bahamondes L, Fernandes A, Bahamondes MV, Juliato CT, Ali M, Monteiro I. Pregnancy outcomes associated with extended use of the 52-mg 20 µg/day levonorgestrel-releasing intrauterine system beyond 60 months: A chart review of 776 women in Brazil. *Contraception* 2018;97:205–9. doi:10.1016/j.contraception.2017.10.007.
- [7] Creinin MD, Schreiber CA, Turok DK, Cwiak C, Chen BA, Olariu AI. Levonorgestrel 52 mg intrauterine system efficacy and safety through 8 years of use. *American Journal of Obstetrics and Gynecology* 2022 S0002937822003660. doi:10.1016/j.ajog.2022.05.022.
- [8] Hidalgo MM, Hidalgo-Regina C, Bahamondes MV, Monteiro I, Petta CA, Bahamondes L. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. *Contraception* 2009;80:84–9. doi:10.1016/j.contraception.2009.01.004.
- [9] Apter D, Gemzell-Danielsson K, Hauck B, Rosen K, Zurth C. Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies. *Fertility and Sterility* 2014;101:1656–62 e4. doi:10.1016/j.fertnstert.2014.03.004.
- [10] Ortiz M, Croxatto H. The mode of action of IUDs. *Contraception* 1987;36:37–53.
- [11] Lippes J. Contraception with intrauterine plastic loops. *American Journal of Obstetrics and Gynecology* 1965;93:1024–30.
- [12] Food and Drug Administration. Kyleena (levonorgestrel-releasing intrauterine system) package insert. 2016.
- [13] Bahamondes L, Faundes A, Sobreira-Lima B, Lui-Filho JF, Pecci P, Matera S. TCu 380A IUD: a reversible permanent contraceptive method in women over 35 years of age. *Contraception* 2005;72:337–41. doi:10.1016/j.contraception.2004.12.026.
- [14] Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, et al. Safety and efficacy in parous women of a 52-mg levonorgestrel-mediated intrauterine device: a 7-year randomized comparative study with the TCu380A. *Contraception* 2016;93:498–506. doi:10.1016/j.contraception.2016.02.024.
- [15] Sivin I. Utility and drawbacks of continuous use of a copper T IUD for 20 years. *Contraception* 2007;75:S70–5. doi:10.1016/j.contraception.2007.01.016.
- [16] United Nations Development Program, United Nations Population Fund, World Health Organization, World Bank, Special Programme of Research Development and Research Training in Human Reproduction. Long-term reversible contraception twelve years of experience with the TCu380A and TCu220C. *Contraception* 1997;56:341352 S0010782497001868. doi:10.1016/S0010-7824(97)00186-8.

- [17] Ali M, Akin A, Bahamondes L, Brache V, Habib N, Landoulsi S, et al. Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant. *Human Reproduction* 2016;31:2491–8. doi:10.1093/humrep/dew222.
- [18] McNicholas C, Swor E, Wan L, Peipert JF. Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration–approved duration. *American Journal of Obstetrics and Gynecology* 2017;216:586 e1–586.e6. doi:10.1016/j.ajog.2017.01.036.
- [19] Wu JP, Pickle S. Extended use of the intrauterine device: a literature review and recommendations for clinical practice. *Contraception* 2014;89:495–503. doi:10.1016/j.contraception.2014.02.011.
- [20] Curtis KM. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65. doi:10.15585/mmwr.rr6503a1.
- [21] Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstetrics and Gynecology* 2012;120:21–6. doi:10.1097/AOG.0b013e318259565a.
- [22] Mornar S, Chan L-N, Mistretta S, Neustadt A, Martins S, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. *American Journal of Obstetrics and Gynecology* 2012;207:110 e1–110.e6. doi:10.1016/j.ajog.2012.05.002.
- [23] Lazowitz A, Aquilante CL, Sheeder J, Guiahi M, Teal S. Relationship between patient characteristics and serum etonogestrel concentrations in contraceptive implant users. *Contraception* 2019;100:37–41. doi:10.1016/j.contraception.2019.03.045.
- [24] Winner B, Buckel C, Secura GM. Effectiveness of long-acting reversible contraception. *New England Journal of Medicine* 2012;10.
- [25] ACOG Committee Opinion 735: Adolescents and long-acting reversible contraception: implants and intrauterine devices. *Obstetrics and Gynecology* 2018;131(10).
- [26] Teal SB, Turok DK, Chen BA, Kimble T, Olariu AI, Creinin MD. Five-year contraceptive efficacy and safety of a levonorgestrel 52-mg intrauterine system. *Obstetrics and Gynecology* 2019;133:63–70. doi:10.1097/AOG.0000000000003034.
- [27] Westhoff CL, Keder LM, Gangestad A, Teal SB, Olariu AI, Creinin MD. Six-year contraceptive efficacy and continued safety of a levonorgestrel 52 mg intrauterine system. *Contraception* 2020;101:159–61. doi:10.1016/j.contraception.2019.10.010.
- [28] Nexplanon- etonogestrel implant. US Food and Drug Administration (FDA) approved product information. Revised July, 2021. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021529s0111bl.pdf (Accessed on June 29, 2022).
- [29] Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infectious Disease in Obstetrics and Gynecology* 2012;2012:1–15. doi:10.1155/2012/890160.
- [30] Nanda K, Stuart GS, Robinson J, Gray AL, Tepper NK, Gaffield ME. Drug interactions between hormonal contraceptives and antiretrovirals. *AIDS* 2017;31:917–52. doi:10.1097/QAD.0000000000001392.
- [31] Lazowitz A, Davis A, Swartz M, Guiahi M. The effect of carbamazepine on etonogestrel concentrations in contraceptive implant users. *Contraception* 2017;95:571–7. doi:10.1016/j.contraception.2017.03.004.
- [32] Leticée N, Viard J-P, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception* 2012;85:425–7. doi:10.1016/j.contraception.2011.09.005.
- [33] Lazowitz A, Pena M, Sheeder J, Teal S. Effect of topiramate on serum etonogestrel concentrations among contraceptive implant users. *Obstetrics and Gynecology* 2022 Publish Ahead of Print. doi:10.1097/AOG.0000000000004697.
- [34] ACOG. ACOG Practice Bulletin 206: use of hormonal contraception in women with coexisting medical conditions 2019;133:23.
- [35] Gbolade B. Failure of Implanon on antituberculous therapy. *Open Access Journal of Contraception* 2010;103. doi:10.2147/OAJC.S12194.
- [36] Tufa TH, Fessehaye A, Abubeker FA. Etonogestrel contraceptive implant failure in a woman taking rifampin: a case report. *Contraception and Reproductive Medicine* 2022;7:5. doi:10.1186/s40834-022-00172-1.
- [37] Chevreau J, Krief D, Abou Arab O, Zitoun M, Foulon A, Sergent F, et al. Factors associated with removal difficulties of etonogestrel-containing contraceptive implants (Nexplanon®). *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2018;224:81–4. doi:10.1016/j.ejogrb.2018.03.019.
- [38] UCSF Beyond the Pill COVID-19 LARC resources. 2020. <https://beyondthepill.ucsf.edu/sites/beyondthepill.ucsf.edu/files/UCSF%20BtP%20COVID-19%20LARC%20Guidance%204-22-20.pdf> (Accessed June 29, 2022)
- [39] Benson LS, Madden T, Tarleton J, Micks EA. Society of Family Planning interim clinical recommendations: contraceptive provision when healthcare access is restricted due to pandemic response. *Society of Family Planning* 2020. doi:10.46621/UYGR2287.