Long-Acting Reversible Contraception: A Review in Special Populations

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Almost half of the pregnancies in the United States are unintended. Currently available contraceptive methods are highly efficacious, but the most commonly used methods rely on patients for appropriate use. There has been a push to advocate for long-acting reversible contraceptives (LARCs) as first-line methods because they are placed by medical professionals and are the most effective form of reversible contraception available. There are four LARCs currently available in the United States: the Copper T intrauterine device, two forms of the levonorgestrel intrauterine system, and the etonogestrel subdermal implant. Once inserted, they can be left in place for 3–10 years, depending on the device. Some of these devices have been available for a number of years, but their use is limited in the United States due to controversies and misconceptions. A MEDLINE search from 1990–2012 was conducted to identify articles describing the use of LARCs in populations with limited data, including postpartum women, adolescents and nulliparous women, and women with sexually transmitted infections, including human immunodeficiency virus (HIV). Health care provider safety concerns surrounding intrauterine device (IUD) expulsions and infection are issues for use in adolescents and nulliparous women. Concern regarding IUD expulsion in the postpartum population questions the benefit of immediate versus delayed insertion, and the progestin effect in the levonorgestrel IUD and etonogestrel implant is of theoretic concern for breastfeeding women. In women with HIV, concerns have been raised about increased viral shedding with the IUD and drug interactions with the progestin methods. Many misconceptions surrounding LARCs are unfounded, but individual risk factors may leave LARC users at risk of unintended pregnancy if not addressed properly.

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Approximately 49% of pregnancies in the United States are unintended, resulting in adverse consequences for mother and child, high abortion rates, and a total estimated cost to tax payers of $9.6–$12.6 billion/year.[1] Currently-available contraception is highly effective when used correctly. The probability of pregnancy when using any contraceptive method is 12% within the first year of use.[2] Poor adherence may contribute to the high rate of unintended pregnancies, with an estimated 48% of unintended pregnancies occurring in women using contraception.[3] One goal of current federal initiatives, such as Healthy People 2020 and the Affordable Care Act, is to increase the number of Americans with health insurance and insurance coverage for contraceptives, thus aiming to improve rates of intended pregnancies.[4, 5]

There are four long-acting reversible contraceptive (LARC) methods currently available in the United States. The Copper T 380A Intrauterine Device (Cu-IUD, ParaGard; Teva, Sellersville, PA, USA) was first approved for use by the U.S. Food and Drug Administration (FDA) in 1988. Approval of the Levonorgestrel-Releasing Intrauterine System (LNG-IUD, Mirena; Bayer

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HealthCare, Wayne, NJ, USA) followed in 2000, with the etonogestrel single-rod implant (Implanon; Merck, Whitehouse Station, NJ, USA) approved in 2006. Implanon has been phased out and replaced with Nexplanon (Merck), a single-rod, radiopaque etonogestrel implant approved in 2011. A lower-dose LNG-IUD (low-dose LNG-IUD) (Skyla; Bayer HealthCare) received approval in January 2013.

LARCs are the most effective reversible methods of contraception available (Table 1).[1] Advantages compared with other reversible contraceptive methods include the limited effort needed by the user to maintain long-term and effective protection, rapid return to fertility following device removal, and lack of interference with lactation.[7] Their user-friendliness has earned them the nickname of "get it and forget it" methods.[8] LARCs have also been modeled to be cost effective, and could reduce total costs spent on unintended pregnancies and contraception by $288 million/year.[1] Despite the positive attributes of LARCs and their increasing usage, they remain an underutilized contraceptive method. The rate of use for intrauterine devices (IUDs) in 2010 was 5.6%, an increase from 0.8% in 1995.[2] Reasons cited for lack of utilization of LARCs include patients' limited knowledge of and attitudes toward these methods, provider practice patterns, and high initial up-front costs associated with the LARC itself and the placement procedure.[9] Usage of the single-rod contraceptive implant has yet to be tracked. The American College of Obstetricians and Gynecologists (ACOG) and the U.S. Medical Eligibility Criteria for Contraceptive Use (U.S. MEC) have recommendations in place for LARC use in women.[7, 10] The U.S. MEC adapted their recommendations from the World Health Organization, which provides guidance for family planning needs globally.[11] The purpose of this manuscript is to raise awareness about specific patient populations in whom the use of LARCs is under-studied.

Copper T380A IUD

The Cu-IUD is FDA-approved for contraception up to 10 years and is used off-label as a highly effective, but underutilized method of emergency contraception (Table 2).[12] The T-frame is made of polyethylene with barium sulfate to aid in device detection under radiography.[13] A 176-mg copper wire is coiled along the vertical stem with a 68.7-mg copper collar on each side of the horizontal arms. The Cu-IUD is a nonhormonal contraceptive device in which the foreign body effect of the IUD frame and the presence of copper prevent pregnancy.[6] The foreign body effect causes a sterile inflammatory reaction; impairs implantation; is toxic to sperm and ova; acts to impair sperm motility, capacitation, and survival; and increases sperm phagocytosis. Capacitation is the process by which the glycoprotein coat of the spermatozoa undergoes modification after reaching the fallopian tube to allow for fertilization of an ovum. The Cu-IUD causes an increase in copper ions, enzymes, prostaglandins, and macrophages in uterine and tubal fluids, impairing sperm function and preventing fertilization. Failure rates are similar to sterilization (Table 1).[14] The most common adverse effects are heavy menstrual bleeding, dysmenorrhea, expulsion, and cramping and/or pain with insertion.[6] Serious adverse effects include infection, uterine perforation, and pregnancy complications. Return to fertility is immediate on removal of the device.[8] The 2013 average wholesale price (AWP) of the Cu-IUD is $718.[15] However, AWP does not include cost of insertion and office visit, which can increase the upfront expense of IUD insertion.

Levonorgestrel-Releasing IUD

The LNG-IUD is FDA-approved for contraception up to 5 years in parous women and for treatment of menorrhagia (Table 2).[16] Studies investigating the use of the LNG-IUD as emergency contraception are ongoing.[17] The LNG-IUD is a T-shaped polyethylene frame with a 52-mg reservoir of levonorgestrel.[18] For the first 5 years of use, the IUD releases 20 μg/day of levonorgestrel. The LNG-IUD prevents fertilization through the same foreign body reaction produced by the Cu-IUD, resulting in a sterile inflammatory reaction in the intrauterine environment.[6] In addition, the progestin levonorgestrel works locally to thicken the cervical mucus, suppress proliferation of the endometrium, and impair sperm function. Levonorgestrel may also be absorbed systemically, which impairs ovulation. Due to suppression of endometrial proliferation, menstrual bleeding patterns can be altered. Gross annual rates of amenorrhea ranging from 2.5–6.6/100 women/year have been reported.[19] The LNG-IUD failure rate is similar to sterilization and the Cu-IUD (Table 1).[14] Common and severe adverse effects are similar to the Cu-IUD, except for bleeding

Table 1. Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year. United States[5]

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[c]
Method (1)	Typical Use[a] (2)	Perfect Use[b] (3)	(4)
No method[d]	85	85	
Spermicides[e]	28	18	42
Fertility awareness-based methods	24		47
Standard Days method[f]		5	
TwoDay method[f]		4	
Ovulation method[f]		3	
Symptothermal method		0.4	
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Condom[g]			
Female (fc)	21	5	41
Male	18	2	43
Diaphragm[h]	12	6	57
Combined pill and progestin-only pill	9	0.3	67
Evra patch	9	0.3	67
NuvaRing	9	0.3	67
Depo-Provera	6	0.2	56
Intrauterine contraceptives			
ParaGard (copper T)	0.8	0.6	78
Mirena (levonorgestrel)	0.2	0.2	80
Implanon	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100
Emergency Contraceptives: Emergency contraceptive pills or insertion of a copper intrauterine contraceptive after unprotected intercourse substantially reduces the risk of pregnancy.[i]			
Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.[j]			

[a]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides and the diaphragm are taken from the 1995 National Survey of Family Growth corrected for underreporting of abortion; estimates for fertility awareness-based methods, withdrawal, the male condom, the pill, and Depo-Provera are taken from the 1995 and 2002 National Survey of Family Growth corrected for underreporting of abortion. See the text for the derivation of estimates for the other methods.

[b]Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. See the text for the derivation of the estimate for each method.

[c]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

[d]The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[e]Foams, creams, gels, vaginal suppositories, and vaginal film.

[f]The Ovulation and TwoDay methods are based on evaluation of cervical mucus. The Standard Days method avoids intercourse on cycle days 8 through 19. The Symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.

[g]Without spermicides.

[h]With spermicidal cream or jelly.

[i]Ella, Plan B One-Step and Next Choice are the only dedicated products specifically marketed for emergency contraception. The label for Plan B One-Step (one dose is 1 white pill) says to take the pill within 72 hours after unprotected intercourse. Research has shown that all of the brands listed here are effective when used within 120 hours after unprotected sex. The label for Next Choice (one dose is 1 peach pill) says to take one pill within 72 hours after unprotected intercourse and another pill 12 hours later. Research has shown that that both pills can be taken at the same time with no decrease in efficacy or increase in side effects and that they are effective when used within 120 hours after unprotected sex. The Food and Drug Administration has in addition declared the following 19 brands of oral contraceptives to be safe and effective for emergency contraception: Ogestrel (one dose is 2 white pills), Nordette (one dose is 4 light-orange pills), Cryselle, Levora, Low-Ogestrel, Lo/Ovral, or Quasence (one dose is 4 white pills), Jolessa, Portia, Seasonale or Trivora (one dose is 4 pink pills), Seasonique (one dose is 4 light-blue-green pills), Enpresse (one dose is 4 orange pills), Lessina (one dose is 5 pink pills), Aviane or LoSeasonique (one dose is 5 orange pills), Lutera or Sronyx (one dose is 5 white pills), and Lybrel (one dose is 6 yellow pills).

[j]However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 mo of age.

Table 2. Description of Long-Acting Reversible Contraceptives

Product	Dose	Mechanism of action	FDA-approved	Off-label	Bleeding pattern	Duration (yrs)
Nonhormonal T380A Copper T IUD[6, 13]	–	Foreign body effect; sterile inflammatory reaction impairs sperm motility, capacitation, and survival	Contraception	Emergency contraception	Regular periods possible Heavy Bleeding	10
Levonorgestrel IUS[6, 17, 18]	20 μg/day	Foreign body effect; thickening of cervical mucus, suppression of endometrial proliferation, impaired sperm function	Heavy Menstrual Bleeding Contraception	Emergency contraception[a]	Light bleeding to amenorrhea	5
Low dose levonorgestrel IUS[20]	14 μg/day (after 24 days); 10 μg/day (after 60 days); 5 μg/day (after 3 years)	Foreign body effect; thickening of cervical mucus, suppression of endometrial proliferation, impaired sperm function	Contraception	None	Light bleeding to amenorrhea	3
Etonorgestrel implant[6, 22]	60–70 μg/day (5–6 wks); 25–30 μg/day (after 3 yrs)	Ovulation suppression, changes in cervical mucus, endometrium alteration	Contraception	None	Irregular bleeding	3

IUD = intrauterine device; IUS = intrauterine system; FDA = United States Food and Drug Administration.
[a]Currently being investigated.

patterns, which begin as light and irregular and may progress to amenorrhea with increasing duration of use.[6] Return to fertility is immediate on removal of the device; 80% of women conceive within the 12 months following LNG-IUD removal.[8, 18] The 2013 AWP of the LNG-IUD is $844.[15]

Low-Dose Levonorgestrel-Releasing IUD

The low-dose LNG-IUD is FDA-approved for contraceptive use for up to 3 years in parous and nulliparous women (Table 3).[20] Similar to the LNG-IUD, the low-dose version is a T-shaped polyethylene frame with a reservoir but contains only 13.5 mg of levonorgestrel.[20] The frame measures 28 mm across and 30 mm long, which is slightly smaller than the LNG-IUD (32 mm across and 32 mm long).[18, 20] The low-dose LNG-IUD delivers levonorgestrel at a rate of ~14 μg/day 24 days post insertion, which decreases to 10 μg/day after 60 days and to 5 μg/day by 3 years. The average release rate is 6 μg/day during its 3-year insertion period. Although the exact mechanism of contraceptive effect has not been conclusively demonstrated, it is likely to be similar to the LNG-IUD.[6, 20] Common and severe adverse reactions are similar to the LNG-IUD.[20, 21] Approximately 77% of women wanting to become pregnant conceived within 1 year post IUD removal. The 2013 AWP of the low-dose LNG-IUD is $780.[15]

Etonogestrel Single-Rod Contraceptive Implant

The etonogestrel implant is FDA-approved for contraception up to 3 years (Table 3).[22] The etonogestrel implant is a single, rod-shaped, radiopaque implant that contains 68 mg of etonogestrel that is inserted subdermally under the skin at the inner side of the nondominant upper arm.[22] Etonogestrel is the active metabolite of the progestin desogestrel. After insertion, 60–70 μg/day of etonogestrel is released for 5–6 weeks and gradually decreases to 25–30 μg/day by the end of the third year. Contraceptive effects are achieved by ovulation suppression, changes in the cervical mucus to impair sperm penetration, and endometrium alteration to decrease risk for implantation should ovulation occur.[6] After implant removal, there is quick return to fertility; etonogestrel levels become undetectable in most users within 1 week and ovulation occurs within 6 weeks.[6] Failure rates are similar to sterilization and aforementioned

Table 3. Selected Populations for the United States Medical Eligibility Criteria

	Implant		LNG-IUD		Cu-IUD	
Condition	I	C	I	C	I	C
Age (Adolescents)						
Menarche to <18	1		–		–	
Menarche to <20	–		2		2	
HIV						
High Risk	1		2	2	2	2
HIV infected	1		2	2	2	2
AIDS	1		3	2	3	2
Clinically well (on therapy)		–	2	2	2	2
Antiretroviral Therapy, NRTI	1		2/3	2	2/3	2
NNRTI	2		2/3	2	2/3	2
Ritonavir-boosted PI	2		2/3	2	2/3	2
Parity						
Nulliparity	1		2		2	
Parity	1		1		1	
Postpartum						
Breastfeeding <1 mo	2		–		–	
Breastfeeding ≥1 mo	1		–		–	
Not breastfeeding <21 days	1					
Not breastfeeding >21 days	1					
<10 min after placenta delivery[a]	–		2		1	
10 min after placenta delivery-4 wks[a]	–		2		2	
≥4 wks[a]	–		1		1	
Puerperal sepsis	–		4		4	
STIs/PID						
Past PID/No risk for STI/with subsequent pregnancy	1		1	1	1	1
Past PID/No risk for STI/no subsequent pregnancy	1		2	2	2	2
Current PID	1		4	2	4	2
Current purulent cervicitis or chlamydial infection or gonorrhea	1		4	2	4	2
Other STIs (excluding HIV and hepatitis)	1		2	2	2	2
Vaginitis (including BV and Trich)	1		2	2	2	2
Increased risk for STIs	1		2/3	2	2/3	2

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine device; Cu-IUD = copper T 380A intrauterine device; NRTI = nucleoside reverse transcriptase inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitor; PID = pelvic inflammatory disease; STI = sexually transmitted infection; BV = bacterial vaginosis; Trich = trichomonas vaginalis.
I = initiation of contraceptive method; C = continuation of contraceptive method; 1 = A condition for which there is no restriction for use of the contraceptive method; 2 = A condition for which the advantages of using a method generally outweigh the theoretic or proven risks; 3 = A condition for which the theoretic or proven risks usually outweigh the advantages of using the method; 4 = A condition that represents an unacceptable health risk if the contraceptive method is used.
[a]Includes post-cesarean patients.
(Modified from Ref. 9).

IUDs (Table 1).[14] There is an inverse relationship between etonogestrel serum concentration and body weight,[22] and the contraceptive efficacy of the implant has not been studied in overweight women (>130% ideal body weight). This is important because it may place a woman at risk for an unintended pregnancy, especially as serum levels decline after implant insertion. In a subgroup analysis of implant users, only one unintended pregnancy among 1377 women-years of implant use was reported, which occurred in an obese patient (body mass index ≥30 kg/m^2).[23] Failure rates for the implant did not differ based on body mass index comparisons, but there is need for additional information in this population. Common side effects include bleeding irregularities, with 33.6% of users experiencing infrequent bleeding, 22.2% experiencing amenorrhea, and 17.7% experiencing prolonged bleeding, and pain with insertion.[22] The 2013 AWP of the etonogestrel implant is $791.[15]

The Contraceptive CHOICE Project

A substantial portion of the available LARC clinical trial literature evaluated devices that are no longer available in the United States, enrolled select populations, and were conducted in countries where LARC use is more prevalent and overall reproductive care differs from the United States. The Contraceptive CHOICE project, which is the largest study of currently available LARCs in the United States, was a prospective

cohort study of 9256 women in the St. Louis, Missouri, region. In the context of federal initiatives designed to reduce the rate of unintended pregnancies, the Contraceptive CHOICE project has been highly publicized and is at the forefront of contraception management. The objectives of this study were to promote the use of LARC methods, and provide no-cost contraception.[24] Eligible women were 14–45 years of age who were in a heterosexual relationship, desired reversible contraception, were willing to start and/or change their current contraceptive method, and had no desire to become pregnant within 1 year. All women were provided any reversible contraceptive method of their choice at no cost for 3 years (first 5090 women) or 2 years (remaining women). Brief documents describing the effectiveness and safety of LARCs were provided and women underwent evidence-based, structured contraceptive counseling before choosing any reversible contraceptive method. At baseline, the CHOICE participants were young (mean age = 25), black (51%), had a high school education or less (35%), had financial difficulties (39%), were on public assistance (37%), and were uninsured or receiving public insurance (56.9%). It is important to note that these participants were low-income and at high risk for unintended pregnancies; 3871 participants (41.8%) had an abortion either before or at the time of project CHOICE enrollment. Recruitment took place at university, community, and abortion clinics; 83.8% of participants were enrolled at university and community clinics, and 16.2% were enrolled at two abortion clinics. Of all participants, 75% chose to use a LARC. Those aged 14–17 and 18–20 years selected a LARC as their chosen contraceptive method 69% and 61% of the time, respectively. Among participants 15–19 years old, the birth rate was 6.3/ 1000, compared with a national birth rate of 34.3/1000 for the same age group.[24, 25] Abortion rates were significantly lower in the project CHOICE cohort compared with the regional cohort, 4.4–7.5/1000 versus 13.4–17/1000, respectively ($p<0.001$) and lower than the national rate of 19.6/1000.[24] Repeat abortions also declined over time ($p=0.002$). Some limitations to this study include generalizability; many study participants had characteristics that place them at high risk for unintended pregnancy. Also, access to abortions is limited by state laws, cost, and availability of clinics performing abortions; abortion rates are specific to geographic area.

In another analysis of project CHOICE, women and adolescents in the LARC arm experienced lower cumulative contraceptive failure rates than participants in the arm cumulatively evaluating use of contraceptive pills, patches, and rings.[26] Failure rates at years 1, 2, and 3 were significantly lower in those using LARCs (0.3%, 0.6%, 0.9%) compared with users of the pill, patch, or ring (4.8%, 7.8%, 9.5%, $p<0.001$). These data suggest that women and adolescents who use the pill, patch, or ring are at increased risk of unintended pregnancy compared with users of LARC.

A retrospective analysis of project CHOICE determined the long-term (12 mo) continuation and satisfaction rates of 2846 LARC users compared with other contraception methods ($n=1321$).[27] Patients were analyzed if they received their baseline contraceptive method during the first 3 months of the study and reached their 12-months time point follow-up telephone survey. The continuation rate for all LARC methods was 86.2% compared with 54.7% for nonLARC methods. Satisfaction rates (stated as "very satisfied or somewhat satisfied") were 83.7% for all LARC methods compared with 52.7% for nonLARC methods.

Special Populations

Postpartum Women

With the option for immediate postplacental insertion, LARCs offer mothers the option of long-term contraception that is reversible, low maintenance, and cost-effective.[6] Contraception during the postpartum period is essential for the prevention of unintended pregnancies and short birth intervals, which can lead to negative health outcomes for mothers and children.[28] Because ovulation can occur as early as 25 days postpartum in nonbreastfeeding women, there is an apparent need to begin contraception shortly after giving birth. In addition, the hematologic changes that occur normally during pregnancy, the postpartum period, and breastfeeding should be considered when selecting postpartum contraception. Estrogen is not indicated before 21 days postpartum in nonbreastfeeding women because of an increased risk of venous thromboembolism (VTE) and postpartum thrombophlebitis. Estrogen should not be used before 42 days postpartum in women with risk factors for VTE. In breastfeeding women without risk factors for VTE, estrogen should not be used until 30–42 days

postpartum.[28] Reversible, nonhormonal contraceptive options for postpartum women include spermicides, barrier methods, lactational amenorrhea method, and the Cu-IUD.[6, 10] Progestin-only contraceptives, including the etonogestrel implant, LNG-IUD, medroxyprogesterone acetate (DMPA) and progestin-only pills are considered safe and effective hormonal options for breastfeeding women by both the U.S. MEC and ACOG (see Table 3).[6, 28, 29] These recommendations differ from the World Health Organization (category 3—use not recommended unless other methods not available) due to the limited research in infants less than 6 weeks of age.[11] Infant exposure to and effect on breast milk production by progestins are concerns about LNG-IUD and etonogestrel implant use, as is the potential for exogenous progestin to interfere with successful establishment of lactation.[6] Efficacy of IUDs during the postpartum period may be diminished because uterine involution increases the risk of expulsion. Safety concerns associated with IUDs, such as uterine perforation, pain, and bleeding, should also be taken into consideration during the postpartum period.[30]

Postpartum Insertion Timing and Safety

A systematic review of 15 Cu-IUD studies determined if postpartum IUD insertion was associated with higher rates of expulsion and increased risk of adverse events, such as perforation, pain, and bleeding.[30] Immediate postpartum insertion (within 10 min) was compared with interval (≥6 wks postpartum) or later postpartum insertion periods. It found that immediate postpartum IUD insertion did not increase the risk of complications. Expulsion rates were lower in the interval group than in the immediate group, and both were lower than in the delayed postpartum group. Cesarean births were associated with lower expulsion rates than vaginal deliveries. Although adverse effects (perforation, pain, bleeding, and infection) did occur in all insertion groups, there were no increased rates at any of the time periods (immediate, interval or later postpartum) or between vaginal or cesarean births across all groups. Two U.S. studies were included in this systematic review.[31, 32] One study with immediate IUD insertion (within 55 hrs) demonstrated 7 expulsions in 82 patients who had their IUD inserted within 30 minutes versus 10 expulsions in 18 patients who had their IUD inserted from 31 minutes–55 hours.[31] This study, which is part of the systematic review, demonstrates that earlier insertion (within 30 min) is preferred, however, longer time frames may be considered acceptable if alternatives for contraceptives cannot be found. It is important to note, however, for this particular study the low number of patients who underwent IUD insertion beyond 30 minutes. The IUDs were removed in five cases because of pain, two cases because of bleeding, and there was one case of postpartum endometritis. The second study, which did not look at immediate IUD insertion patients, demonstrated an expulsion rate of 6.5% in nonpostpartum patients (>8 wks) compared with 10.8% in patients 4–8 weeks postpartum.[32] The pain and bleeding rates were 16.9% versus 17.3% in the over 8 weeks and 4–8 weeks groups, respectively. Limitations to the systematic review included the inability to determine an actual risk estimate because of variation across studies, the variable definition of expulsion and later postpartum insertion periods, and the wide range of countries and providers represented.

Similarly, a prospective feasibility study evaluated the expulsion rate among 90 women who selected to use the Cu-IUD after a cesarean section.[33] Women were seen for follow-up at 6 weeks and 6 months. No IUD expulsions were reported by patients or recorded in medical records during the study time frame; only 48 women were seen at the 6-week visit and 42 at the 6-months contact. Of these 42 women, 80% reported being "happy" or "very happy" with their IUD, no requests for IUD removal were made at this time. Cramping or heavy bleeding during menses was reported by 23 (55%) of the participants. Although this study was limited by attrition and self-reporting bias, the findings demonstrate that IUD use is acceptable to postpartum women and carries a low risk of expulsion.

There are only two published studies that have evaluated the insertion timing of the LNG-IUD in the postpartum period.[34, 35] One pilot study examined immediate insertion (within 10 min of placental delivery) in 19 eligible women following vaginal delivery. Only two expulsions occurred by 10 weeks (10.5%).[35] This is similar to other immediate postplacental Cu-IUD insertion studies, with 6-month and 1-year expulsion rates of 8.5% and 12.3%, respectively.[31, 36] A second, larger study compared the use of the LNG-IUD at 6 months in 102 women with immediate (within 10 min of

placental delivery) or delayed (6–8 wks postpartum) insertion following a vaginal delivery.[34] Fifty women of the 51 women in the immediate-insertion group had their IUD successfully placed, and all 46 women of the 51 who were randomized to the delayed insertion group returned for their insertion and had their IUD successfully placed. Most patients in each group reported no pain with insertion. During the 6 months follow-up period, expulsions occurred in 12 women (24%) in the immediate group compared with 2 (4.4%) in the delayed group (p=0.08). After adjusting for replacement of devices and patients lost to follow-up, rates of IUD use at 6 months were 84.3% (43/51) compared with 76.5% (39/51) in the immediate and delayed groups, respectively (p=0.32). The high expulsion rates in the immediate-insertion arm (24%) could be attributed to the insertion procedure. This includes the use of the LNG-IUD inserter, instead of manual insertion or forcep-guided insertion, or inexperience with delayed insertion for some of the providers (however, confirmation of IUD placement was done by ultrasound).

Breastfeeding

There are two conflicting reports on the status of breastfeeding duration with LNG-IUD use.[37, 38] However, only one study evaluated immediate insertion (<10 min) and the duration of breastfeeding.[37] This randomized study compared breastfeeding continuation after delivery in women who had immediate (<10 min postplacental delivery) or delayed (6–8 wks) IUD insertion and followed them for up to 6 months.[37] Breastfeeding was initiated in 32/50 (64%) women in the immediate group and in 27/46 (59%) women in the delayed group. Breastfeeding at 6 months negatively correlated with a less than high school education and African-American race (p=0.06). Mean duration of lactation was 5 weeks (0.5–27 wks) in the immediate group compared with 8.5 weeks (0.1–43 wks) in the delayed group. More women continued to breastfeed at 6–8 weeks in the delayed group compared with the immediate group (16/46 [35%] vs 15/50 [30%], p=0.62), 3 months (13/46 [28%] vs 7/50 [14%], p=0.13), and 6 months (11/46 [24%] vs 3/50 [6%], p=0.2). Although these data were collected prospectively, extrapolation of the results may be limited by self-reporting of breastfeeding behaviors and failure to account for breastfeeding difficulties, return to work, social or cultural differences, or support. In addition, infant factors, such as development or number of feeds, were not reported.

A prospective, randomized, controlled trial compared the effects of the LNG-IUD with the Cu-IUD on breastfeeding patterns and infant growth and development during the first postpartum year.[38] Women planning on breastfeeding for 1 year were randomized to the LNG-IUD (n=163) or Cu-IUD (n=157) group with insertion at 6–8 weeks postpartum. There were no significant differences between the two groups with regard to the average number of feedings/24 hours; the mean duration of full breastfeeding was comparable at 149 days for LNG-IUD and 160 days for Cu-IUD. No significant differences existed in infant weight, length, or developmental testing between the two groups. At the end of the first postpartum year, IUD continuation rates were similar (89.3% for LNG-IUD and 90.9% for Cu-IUD). Limitations to this study include enrollment of women outside of the immediate postpartum period and study location; it was conducted in Egypt, which may have different breastfeeding patterns than the United States.

Two studies have examined the effect of etonogestrel on breastfeeding.[39, 40] Although the etonogestrel implant is recommended to be inserted after 21 days postpartum, a pilot study evaluated the effect of implant insertion on maternal safety during the immediate postpartum period.[39] Women who breastfed exclusively were randomized to either etonogestrel implant 24–48 hours postpartum (n=20) or DMPA (n=20) 6 weeks postpartum. There was no difference in the maintenance of exclusive breastfeeding over 12 weeks postpartum.[39] There was also a nonsignificant trend toward an increase in weight gain for newborns during the first 6 weeks compared with DMPA (1460.50 $\pm$ 621.34 g vs 1035.0 $\pm$ 562.43 g, respectively, p=0.05). Limitations inherent to a pilot population include small sample size and short duration of follow-up. In addition, this study was not designed to assess infant factors as its primary outcome.[39] The second study evaluated milk production and composition in 8 women with healthy, singleton births receiving either the etonogestrel implant or a nonhormonal IUD. There were no statistically significant differences in either end point.[40]

Findings from these studies suggest that the timing of postpartum IUD insertion does not impact efficacy or safety markers and should be considered in all postpartum women.[30, 33–35]

However, delayed postpartum insertion of the LNG-IUD may be preferred in breastfeeding women, as it has been associated with increased breastfeeding duration and maintenance of exclusive breastfeeding.[37] Current recommendations are to place the LNG-IUD 6 weeks postpartum allowing for uterine involution.[18] To date, very small studies show no concerns with safety or breast milk production with the etonogestrel implant, suggesting it can be inserted in the immediate postpartum period regardless of breastfeeding decisions.[39, 40] Because many women engage in sexual intercourse before their 6-week follow-up visit, the need for effective contraception early is evident.

LARC Use in Nulliparous Women and Adolescents

The most common forms of contraception used by adolescents are oral contraceptives and condoms.[4] In 2012, ACOG released an updated committee opinion advocating for the use of LARCs as first-line options for adolescents aged 15–19 years because of increased rates of method failures with the oral contraceptives, patches, and rings.[8, 41] In addition to higher user failure rates, 20% of all teenage mothers give birth again within 2 years, and 15% of all U.S. abortions are performed on adolescents aged 15–19 years.[42, 43] Surveys to young women have revealed low levels of awareness about these methods. However the results of a recent prospective study showed that when educated about LARCS, 70% of all women chose a LARC as their method, with younger women (aged 14–17) choosing the implant.[44, 45] Resistance to IUD use in adolescents and the nulliparous typically center on concerns about lack of familiarity with the methods, costs or access, increases in sexually transmitted infections (STIs) and pelvic inflammatory disease (PID), infertility, and higher expulsion rates.[41] The LNG-IUD is indicated for use in parous women, and the low-dose LNG-IUD is indicated for use in both parous and nulliparous women. The Cu-IUD does not specify parity (see Table 3).[13, 18, 20] The low-dose LNG-IUD has not been included in the U.S. MEC, but should be similar to the LNG-IUD.

There are few randomized, controlled trials of LARC methods specifically in adolescent and nulliparous women. Results from the project CHOICE subgroup analysis revealed that participants under 21 years of age using the ring, patch, or pills had almost twice the risk of unintended pregnancy as older women using the same methods (adjusted hazard ratio [HR] 1.9, 95% confidence interval [CI] 1.2–2.8).[26] However, the contraceptive failure rate did not differ significantly between groups using DMPA or LARCs. The 12-month continuation rates between women aged 14–19, 20–25 and 26 years or older exceeded 75% for all groups.[46] Women aged 14–19 had lower continuation rates compared with older women for both LARC (81% vs 85%, respectively) and nonLARC (53% vs 44%, respectively) methods. Use of contraceptive methods was tracked by allocation and removal logs, pharmacy refill records, and follow-up telephone surveys. The 14–19 age group was less likely to be satisfied with nonLARC (42%) compared with LARC (75%) methods. Limitations to this study include a high risk patient population, structured counseling, and no-cost contraceptives.

The probability of IUD retention and risk factors for removal, expulsion, and infection were evaluated in a retrospective analysis of IUD use in 233 parous or nulliparous women, from menarche to age 21.[47] Women were identified at a gynecology private practice, a community-based, grant funded clinic, or a Title X clinic (designed to provide contraceptive and preventive health services, such as breast and pelvic examinations and STI testing to low-income and uninsured individuals).[47, 48] Median age at time of IUD insertion was 16 years; most patients were parous (69.9%), and at high risk for STIs, with 24% reporting a prior STI. Interestingly, most patients in private practice had IUDs inserted for medical indications such as menorrhagia; the most common indication was contraception in the Title X and community clinics. After adjusting for multiple risk factors, women under 18 years of age were more likely to have their IUD removed ($p<0.001$), and be at greater risk for expulsion or removal (HR = 2.85). Prior STIs conveyed a greater risk of infection (relative risk [RR] = 5.5, $p<0.001$). IUD discontinuation was more closely associated with younger age as opposed to nulliparity. Pain on insertion was not addressed. Limitations to this study include its retrospective nature and specific patient population.

To gain further insight about IUD use in young women, a retrospective analysis of 307 charts of women 19 years or older compared insertion and postinsertion experiences between nulliparous and parous teenagers.[49] Most

patients were nulliparous (77.5%), Caucasian (73.4%), on Medicaid (85.8%), and chose the LNG-IUD (88.3%). The majority of patients had a successful insertion on the first attempt (96.4%). Follow-up data for 172 women revealed 5 IUD expulsions (2.9%); 4 in the nulliparous arm, 1 in the postabortion arm, and none in the parous arm. Post expulsion, all five participants requested and received a second IUD. Ten nulliparous teenagers had their IUD inserted using a paracervical block or IV sedation; all tolerated the procedures. IUD removal for pain and bleeding was more common in the nulliparous compared with parous group (20.9% vs 7.4%, respectively, p=0.05), and PID was diagnosed in 4.6% of all patients. These results demonstrate that IUD insertion and utilization are well tolerated and can be safely inserted in both nulliparous and parous adolescents.

Clinical data on the low-dose LNG-IUD are limited, and there are no available studies that specifically study this IUD. Data on file with the manufacturer evaluated the contraceptive efficacy of the low-dose LNG-IUD in a randomized, open-label, multicenter clinical trial in 1432 women aged 18–35, 556 (38.8%) of whom were nulliparous.[20] During the first year of use, five pregnancies occurred after treatment onset or within 7 days after IUD removal or expulsion. The low-dose LNG-IUD has demonstrated similar efficacy to the LNG-IUD and has shown a trend toward easier placement.[21] However, the hormonal dose studied in this trial for the low-dose LNG-IUD differs from the commercially available product at 12 or 16 μg/day of levonorgestrel.

There is only one study, conducted in Australia that was specifically designed to evaluate the use of the etonogestrel implant in adolescents.[50] In this prospective cohort study of teenage (12–18 yrs old) mothers, the incidence of repeat teenage pregnancies and continuation rates for users of the etonogestrel implant (n=73) were compared with the combination oral contraceptive (COC) pill-DMPA (n=40), or barrier methods/none (n=24). Forty-eight teenagers (35%) had conceived by 24 months; 27% chose the implant, 40% chose COC-DMPA, and 50% chose barrier or none. Etonogestrel implant users became pregnant later compared with COC-DMPA or barrier/none at 23.8, 18.1, or 17.6 months, respectively (p=0.022). Continuation rates at 24 months were higher in the implant group (p<0.01), and the mean duration of implant and COC-DMPA use was 18.7 months (95% CI 17.0–20.3) and 11.9 months (95% CI 9.5–14.3), respectively. Implant users were more likely to be living with the birth father, and ~47% of all mothers had already begun sexual activity by 6 weeks postpartum. Menstrual bleeding with spotting, amenorrhea, or irregular bleeding was highest around 18–21 months (95%, 54%, and 45%, respectively) and lowest around 3 months (58%, 26%, and 11%, respectively). The number of repeat pregnancies, although high, is consistent among this group of women. In addition, this study reinforces the need for early postpartum contraception in this population.[28]

LARC use in nulliparous women and adolescents has been shown to be safe and effective in the sparse studies that are available.[46, 47, 49, 50] There may be higher rates of IUD expulsion and pain in women who are nulliparous, but the rates are still small. LARCs should be considered a first-line agent for most of these patients.

LARC Use in Women with STIs and PID

Theoretic concern exists that during IUD insertion sexually transmitted microorganisms present in the endocervical canal could be transported to the uterine cavity, resulting in PID.[6, 51] Although studies do show a higher rate of PID in women with chlamydia or gonorrhea infection, the risk is still low.[51, 52] In addition, the risk of PID appears to be linked to proximity of insertion, with women having a higher risk within the first 20 days after insertion.[51, 53] Studies on STI association with IUD use are predominately conducted with the Cu-IUD or older IUDs; the LNG-IUD may have a protective effect.[51–54] Insertion recommendations differ depending on timing of PID or STI (Table 3).[10]

A systematic review of six prospective studies compared the risk of developing PID in women who had an STI at the time of IUD insertion with women who did not.[52] Women with chlamydia or gonorrhea infection at the time of insertion were at increased risk of PID compared with women without an infection. The absolute risk of PID was 0–5% for women with STIs and 0–2% for those without. A major limitation to this analysis was that the studies did not directly compare whether IUD insertion or use altered PID risk among women with STIs; it is unknown if the risk of PID is modified by IUD insertion. In addition, summary statistics on PID rates were not evaluated because of the variability of the studies compiled. Initial screening for STIs and diagnostic criteria for PID varied among studies and the overall

number of cases was still small. All the IUDs in this study were the Cu-IUD.

A large, retrospective cohort study compared the incidence of PID within 90 days after IUD insertion between women who were or were not screened for chlamydia or gonorrhea.[55] Of the 57,728 IUD insertions, 47% were unscreened and 19% were screened on the same day of insertion. Overall PID risk was low at 0.54% (95% CI 0.48–0.60). Not screening and any screening had an equivalent risk of PID, and same-day screening was equivalent to prescreening. This study was limited by the retrospective design, clinician discretion, and inability to obtain additional patient characteristics.

Algorithms have been developed to determine if women should be referred for immediate IUD insertion or testing before insertion.[56] An algorithm to identify women at low risk for an STI after IUD insertion was useful when based on age, living with partner, education, bleeding between periods, and behavioral risk score (number of sex partners, condom use). Clinical STI signs did not improve utility of the algorithm.

Mucopurulent cervico-vaginal discharge or known chlamydia or gonorrhea infection should be treated before IUD insertion.[7, 10] If an IUD user experiences an STI postinsertion, it should be treated according to current guidelines; IUD removal is typically not necessary but should be dependent on a women's informed choice and current risk factors for STIs and PID.[7] Women should be counseled on use of a male latex condom in conjunction with these methods to prevent transmission.

LARC Use in Human Immunodeficiency Virus-Positive Women

U.S. women accounted for 10,000 new Human Immunodeficiency Virus (HIV) infections in 2010.[57] Pregnancy in HIV-positive women comes with added risks, including mother-to-child transmission of HIV.[58] Therefore, preventing acquisition of STIs and unintended pregnancies with highly effective contraception compatible with antiretroviral therapy (ART) regimens is important.[6, 10, 59] Dual contraception with a condom has been endorsed by multiple organizations.[10, 59, 60] Despite clear indications for highly effective contraception, theoretic concerns regarding its use and the potential for increased pelvic infections, bleeding, viral shedding, and pharmacokinetic changes with ART have been raised.[61]

A recent observational cohort study over 12 years in 1586 women who were HIV-seropositive (n=1075) or high risk HIV-seronegative (n=511), demonstrated that condoms were the predominant form of contraception in both groups.[61] LARC use increased significantly in the HIV-seronegative group from 4.8% to 13.5% (p=0.02), but not significantly in the HIV-seropositive group, 0.9% to 2.8% (p=0.09). Interestingly, LARC users who were HIV-seronegative, were less likely to use condoms consistently compared with their seropositive counterparts, (HR 0.51, 95% CI 0.32–0.81, p=0.004 vs HR 1.09, 95% CI 0.96–1.23, respectively). This emphasizes the need to continue advocating LARC and condom use in high-risk populations needing protection against unintended pregnancies. See Table 3 for U.S. MEC guidelines for LARC use in women at high risk of acquiring HIV, the HIV-seropositive, and those on ART.

HIV Disease Progression/Transmission

A systematic review of 26 studies was conducted to determine if HIV-infected women who use hormonal or IUD contraception were at a higher risk of disease progression, HIV transmission or other adverse outcomes.[62] The risk of HIV progression was not increased in eight observational studies for either hormonal contraception (six prospective cohort studies) or LNG-IUD (two descriptive studies). However, one randomized controlled trial did show a nonsignificant increased risk of a death (HR 1.4, 95% CI 0.7–3), but a significant declining CD4 cell count (HR 1.6, 95% CI 1.04–2.3) in hormonal users compared with Cu-IUD users. It is important to note that all these studies used various outcome measures (e.g., death, changes in CD4 count, or RNA viral load) to determine HIV progression. Risk of acquiring an STI among HIV-infected women was demonstrated in one study with 47 patients using the levonorgestrel implant (Norplant) or DMPA. There was a 3-fold increased risk of STIs compared with other contraceptive groups, but a major limitation to this study was the inability to determine if these women were using condoms in addition to the progestin contraceptives. Finally, five studies examined HIV transmission to partners or shedding of HIV-infected cells; no association was found with the Cu-IUD or the LNG-IUD.

Two small descriptive studies with the LNG-IUD in HIV-seropositive women did not demonstrate an increase in genital shedding of HIV or

decrease of CD4 counts.[63, 64] In the larger of the two studies, 12 women were followed for 1 year post IUD insertion; the levels of CD4 lymphocytes at the beginning of the study and 12 months were $0.63 \pm 0.18 \times 10^9$/L and $0.58 \pm 0.15 \times 10^9$/L, respectively (p=nonsignificant).[63] Genital shedding of HIV was unchanged before and during LNG-IUD use. In the smaller study, six women using the LNG-IUD for contraceptive and therapeutic purposes were followed for 12–72 months with CD4 lymphocyte levels similar at baseline, 12, and 24 months ($0.59 \pm 0.29 \times 10^9$/L, $0.56 \pm 0.31 \times 10^9$/L, and $0.47 \pm 0.23 \times 10^9$/L, respectively).[64] Limitations to these studies include small sample size and lack of matched controls.

To assess long-term LNG-IUD use in HIV-seropositive women, 15 women using the LNG-IUD and 25 control subjects matched for age and CD4 lymphocyte count were followed for 5 years.[65] The LNG-IUD remained placed in 12 (80%) members of the LNG-IUD arm; CD4 lymphocyte counts did not differ between the groups (p=0.97). Blood levels of HIV-RNA in women not using ART did not differ significantly at baseline and 1 year between the LNG-IUD (3011 ± 3573 to $12{,}458 \pm 17{,}664$ copies/ml; p=0.27) and control groups ($13{,}118 \pm 27{,}443$ to $28{,}553 \pm 61{,}868$ copies/ml; p=0.25). Limitations to this study include its retrospective nature, small sample size, and overall well-cared for women with HIV.

No clinical trials could be identified that specifically examine adverse clinical outcomes for the etonogestrel implant.[62] Some data exist from the levonorgestrel implant (Norplant) and were discussed in the previous section. Implantable contraception is safe and efficacious in this population, but the risk for drug interactions affecting the efficacy of both antiretroviral drugs and contraceptives exists.

Drug Interactions

Drugs that induce cytochrome P450 (CYP) enzymes can increase the clearance of sex hormones and reduce contraceptive efficacy.[66] The package insert for the LNG-IUD states concern for enzyme-inducing CYP3A4 drugs including ARTs.[18] One study demonstrated similar serum levonorgestrel levels with women on ART compared with those who were not, although the levels did decrease over time.[63] Pharmacokinetic analyses specially designed to look at this have not been done.

Concerns exist about drug interactions between the etonogestrel implant and ART due to hepatic induction of etonogestrel metabolism, resulting in decreased contraceptive efficacy.[66–68] Several case reports have described contraceptive failure with the etonogestrel implant, either in women already on etonogestrel at the time of HIV diagnosis and ART initiation (n=1) or implant initiation after the diagnosis of HIV (n=3).[66–68] There were a total of five pregnancies (three ectopic and two intrauterine pregnancies); two of the ectopic pregnancies were in one woman, with one occurring beyond the 3-year efficacy period of the implant. In all cases, the implant was able to be palpated in the correct location and all pregnancies occurred around 2–2.5 years after implant insertion. All four women were on an efavirenz-containing ART with no other significant interacting drugs noted. It is unknown if this is due to general efavirenz use, time after implant insertion and levels of etonogestrel, or other factors.

In general, women with HIV are candidates for LARC use but should be counseled on the importance of using a male latex condom to prevent transmission of HIV. Use of male latex condoms is especially important for those using the etonogestrel implant and on ART, as a pharmacokinetic interaction may occur leading to decreased contraceptive efficacy. This is of particular importance for efavirenz-based ART, as it is teratogenic.[69]

Conclusion

The use of LARCs in the United States is increasing, and this form of contraception is often recommended as first-line use in most women. Although many of these studies are small and done in other countries, the Contraceptive CHOICE project highlights efficacy and safety in many women, particularly in teenagers and women at high risk for unwanted pregnancies. Many misconceptions for limiting IUD and implant use have been unfounded or have been shown to pose small increased risks; however, individual factors should be reviewed when selecting a method.

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