Review Article

Long-acting reversible contraception for adolescents

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Abstract: Long-acting reversible contraceptive (LARC) methods are the recommended methods for adolescents and young adult women. Etonogestrel subdermal implant, the copper intrauterine device and levonorgestrel intrauterine devices are the currently used LARC methods. LARC methods provide effective contraception by preventing fertilization; however, none has an abortifacient effect. The etonogestrel implant is the most effective method with a Pearl index of 0.05. None of the LARC methods has any adverse effect on bone mineral density. Rare safety concerns associated with intrauterine device use include device expulsion, uterine perforation, pelvic inflammatory disease, and ectopic pregnancy. Fertility resumes rapidly upon discontinuation of LARC method. A number of factors have been shown to be barriers or facilitators of LARC method use by adolescents. This article reviews clinical aspects of use for LARC methods for the primary care medical practitioner.

Keywords: Long-acting reversible contraceptive (LARC); etonogestrel subdermal implant; levonorgestrel intrauterine device; copper intrauterine device

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Introduction

Adolescents continue to be sexually active, with forty two percent of 15–19 year old females in the United States reported to have ever engaged in vaginal intercourse with opposite-sex partner (1). Despite 99.4% of sexually active females reporting ever-using contraception, 75% of pregnancies in this age group during 2011 were unintended (1,2). Condoms, withdrawal, and oral contraceptive pills were the most commonly reported methods of contraception used by female teens during this period (97.4%, 59.7%, and 55.5% respectively) (1). Different user dependent contraceptive methods result in decreased effectiveness due to user errors with typical use. A 2017 study, analyzing data extracted from the National Survey of Family Growth in the United States from 2006-2010 showed that withdrawal, condom, and oral contraceptive pills had a significantly higher probability of failure within 1 year of use compared to non-user dependent long-acting reversible contraception (LARC) (3). Due to their safety and effectiveness, LARC is recommended for use in adolescents by the American College of Obstetricians and Gynecologists, the Center for Disease Control and Prevention, the Society for Adolescent Health and Medicine, and the Society of Family Planning (4-9). LARC is considered a first-line contraceptive choice for adolescents and young adults by the American Academy of Pediatrics; however, LARC was used only by 5.8% of 15–19-year-old females between 2011 and 2015, with 2.8% using intrauterine devices (IUDs) and 3% using the implant (1,10).

Table 1 Levonorgestrel intrauterine devices (LNG-IUDs) (12,17-22)

LNG-IUD (total LNG dose)	US brand name[1]	Effective duration	Initial rate of LNG release	Average rate of LNG release
LNG-IUD (19.5 mg)	Kyleena	5 years	17.5 µg/day	9 µg/day over 5 years
LNG-IUD (52 mg)	Liletta	5 years	19.5 µg /day	14.7 µg/day over 5 years
LNG-IUD (52 mg)	Mirena	5 years	20 µg/day	20 µg/day over 5 years
LNG-IUD (13.5 mg)	Skyla	3 years	14 µg/day	8 µg/day over 3 years

[1], US brands: Kyleena, Mirena, and Skyla, manufactured by Bayer HealthCare Pharmaceuticals, Ind, Whippany, USA. Liletta, manufactured by Allergan, Irvine, California, USA.

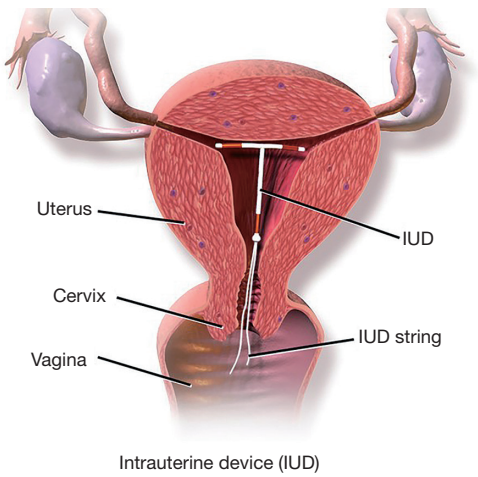

Figure 1 Typical intrauterine device in place. Source: https://commons.wikimedia.org/wiki/File:Blausen_0585_IUD.png. With permission: Blausen.com staff [2014]. Medical gallery of Blausen Medical. WikiJournal of Medicine 2014. doi:10.15347/wjm/2014.010. ISSN 2002-4436-Own work.

Long-acting reversible contraceptive methods

The copper T380A intrauterine device

The copper T380A IUD (ParaGard; CooperSurgical Inc., Trumbull, CT, USA) is a T-shaped device, approximately 32 mm x 36 mm, that is inserted into the uterus through the cervix (7,11). It is made of polyethylene and wrapped with 313.4 mg of copper wire (7,11). The frame contains barium sulfate and is radiopaque (7,11). A monofilament tread extends from the 3 mm diameter tip to aid in detection and removal of the device (11). It is approved by the United States Food and Drug Administration (FDA) for up to 10 years of contraceptive use (7,12).

The hormonal subdermal implant

The etonogestrel subdermal implant (Nexplanon: Merck Sharpe and Dohme, Whitehouse Station, New Jersey, USA) is a 40 mm rod with a 2 mm diameter made of a flexible ethylene vinyl acetate core containing 68 mg of etonogestrel and surrounded by a membrane responsible for the controlled release of etonogestrel (ENG) over 3 years (12,13). It is inserted beneath the dermis on the medial aspect of the upper arm and contains barium sulfate, making it radiopaque (13). The 68 mg of ENG is released gradually starting at 60–70 mcg/day, progressively decreasing to 25–30 µg/day by the third year of use (14).

Hormonal intrauterine devices

The levonorgestrel intrauterine device (LNG-IUD) consists of a T-shaped device, approximately 32 mm × 32 mm, that is inserted into the uterus through the cervix (7,15,16). It is made of polyethylene and contains a hormone reservoir around the vertical portion of the device (7,15,16). The reservoir is made of levonorgestrel and silicone, and contains a specific amount of levonorgestrel to be released gradually overtime (7,15,16). The reservoir is surrounded by a membrane that controls the gradual release of hormone (7,15,16). The frame contains barium sulfate, making it radiopaque (7,15,16). A monofilament thread extends from the vertical stem to aid in detection and removal of the device (15). There are four types of LNG-IUDs available in the United States market, each containing a different amount of levonorgestrel and different rate of LNG release (*Table 1*) (17-22). *Figure 1* depicts a typical IUD in place.

Mechanisms of action of LARC methods

LARC methods provide effective contraception by preventing fertilization by different underlying mechanisms of action (*Table 2*) (23-35). With the ENG subdermal implant, the primary mechanism of action is preventing ovulation. ENG interferes with the hypothalamic-pituitary

Table 2 Mechanisms of action of LARC methods (23-35)

Method	Primary mechanism	Secondary mechanism
ENG subdermal implant	Prevention of ovulation by diminishing LH surge	Decreased sperm motility by increased cervical mucus viscosity and thinning of endometrium
LNG-IUD	Thickening of cervical mucus, impaired ability of sperm to fertilize ovum, decidualization and atrophy of endometrial glands	Sterile inflammatory reaction of the endometrium to the presence of IUD, phagocytosis of sperm in the endometrial cavity
Copper IUD	Spermicidal effect of copper, inhibition of sperm mobility, inhibition of ovum migration, direct toxic effect of copper on sperm	Sterile inflammatory reaction of the endometrium to the presence of IUD, phagocytosis of sperm in the endometrial cavity

LARC, long-acting reversible contraceptive; ENG, etonogestrel; LH, luteinizing hormone; LNG-IUD, levonorgestrel intrauterine device.

axis by preventing the luteinizing hormone (LH) surge, resulting in anovulation (23). Anovulation is responsible for 99% of the contraceptive action of the ENG subdermal implant (23). The remaining 1% is due to decreased sperm motility secondary to increased viscosity of cervical mucus, and by thinning the endometrium (23-25).

An IUD present in the uterus is recognized as a foreign body by the immune system and in response, the number of leukocytes in the endometrial cavity and fallopian tubes increases (26,27). The leukocytes can then phagocytose sperm (26,27). Studies have shown that sperms in the endometrial cavity are phagocytosed within 16 hours after intercourse due to this sterile inflammatory response (28). This likely explains the low number of sperms found in fallopian tubes after intercourse in women using IUDs (26).

With the copper IUD, the primary mechanisms of action are its spermicidal effect, inhibition of sperm motility, and inhibition of ovum migration (29,30). A higher copper level in the IUD is associated with increased contraceptive efficacy (29). Copper is released from the IUD into the uterine cavity. When sperm is present, the copper binds tightly to it, decreasing motility and viability (31). Copper binding to sperm can result in the head of the sperm separating from its tail (31,32). Copper causes an enhanced inflammatory response, stronger than the foreign body inflammatory response seen with inert and hormonal IUDs (27). This response leads to further destruction of sperms (29). Copper ions in the intrauterine space alter the endometrium, further decreasing sperm viability and motility (30). A high copper concentration is also found in the cervical mucus (30,33,34) and can inhibit sperm motility (30,35). Studies suggest copper may be similarly toxic to the ovum (32,36). This could explain the finding of fewer ova in the fallopian tubes of copper IUD users, likely caused by leukocytes destroying the ovum as it travels through the fallopian tube (32,36). It is unlikely that the copper IUDs impairs implantation of the blastocysts after fertilization, and there is no evidence to support that the copper IUD is an abortifacient (27,30,33,37,38).

The active ingredient in the LNG-IUD is the synthetic steroid levonorgestrel, a second-generation progestin (39). LNG binds to the progesterone receptor with 3.2 times the relative affinity of *in vivo* progesterone (40,41). Studies show that when LNG is released in the uterus via the IUD, there is a high specific endometrial uptake, while serum concentration remains low (42,43). With the LNG-IUD, the primary mechanism of action is to thicken the cervical mucus, impairing the ability of sperm to fertilize the ovum (44-47). Additionally, LNG causes apoptosis of the endometrial layer by causing an increased expression of Fas antigen and decreased expression of Bcl-2 protein in the cells of the endometrium (27,48). This mechanism causes a decrease in endometrial proliferation and is likely responsible for reducing menses and the effectiveness of the LNG-IUD in treating menorrhagia (27,48). It is unclear if this disruption to the endometrium has the ability to inhibit blastocyst implantation (16). Similar to the copper IUD, there is no evidence that the LNG-IUD is an abortifacient (27,33).

High serum levels of LNG are required to suppress ovulation (16). Given that most of the LNG released by the IUD is taken up by the endometrium, with a low amount entering the serum, an intrauterine dose of 50 μg/day of LNG would be required to raise serum LNG sufficient to cause anovulation (16). The highest concentration of LNG released from currently used IUDs is not more than 20 μg/day. If anovulation is to occur, it is most likely to occur shortly after the IUD is placed, as the concentration of LNG released per day decreases over time. Given the same daily dose of LNG, four different cycle reactions have

Table 3 Effectiveness of LARC methods using the Pearl index (20,52,54,55)

LARC method	Pearl index, per 100 women-years
ENG subdermal implant (Implanon)	0.05 (52)
LNG-52 mg (Mirena)	0.20 (52)
LNG-19.5 mg (Kyleena)	0.31 (95% CI: 0.15–0.57) (20)
LNG-52 mg (Liletta)	0.22 (95% CI 0.08–0.49) (54)
LNG-13.5 mg (Skyla)	0.33 (95% CI: 0.16–0.60) (20,55)
Copper T380A (ParaGard)	0.80 (52)

[1], US brands: Kyleena, Mirena, and Skyla, manufactured by Bayer HealthCare Pharmaceuticals, Ind, Whippany, USA. Liletta, manufactured by Allergan, Irvine, California, USA. Paragard manufactured by CooperSurgical Inc., Trumbull, CT, USA; Implanon manufactured by Merck Sharpe and Dohme, Whitehouse Station, New Jersey, USA. LARC, long-acting reversible contraceptive; LNG, levonorgestrel; ENG, etonogestrel.

been described: (I) anovulation, (II) anovulation with high follicular activity, (III) ovulation with luteal insufficiency, and (IV) normal ovulation (45,46). Early after LNG-IUD insertion, when systemic LNG is higher, cycles can be anovulatory in some women (45,46). Most cycles become ovulatory after the first year of use (45,46,49).

LNG causes a local decrease in prostaglandin production, causing decreased motility of the fallopian tubes and a shortened fertility window (16). The foreign body response triggered by the IUD induces an inflammatory response that results in ovum and sperm apoptosis (16). These mechanisms play an important, but minor role in contraception.

Of the currently available hormonal IUDs, the LNG-IUD 13.5 mg contains the lowest amount of LNG. Serum LNG levels, while on LNG-IUD 13.5 mg are not high enough to suppress ovulation in most women (19). Although, systemic LNG and rates of anovulation were lower with the LNG-IUD 13.5 mg compared to the LNG-IUD 52 mg, the effect of LNG on endometrial proliferation and cervical mucus production remains the same (19). While the degree of ovulatory suppression varies between LNG-IUDs, the degree of cervical mucus thickening is comparable between the LNG-IUD 13.5 mg, 19.5 mg, and 52 mg (16). Thickening of cervical mucus creates a barrier to sperm penetration (29,50). Decidualization and atrophy of the endometrial glands can reduce sperm survival (29,51).

Effectiveness of LARC methods

LARC is the most effective form of birth control for women. Contraceptive effectiveness refers to how well a pregnancy is prevented with the typical use of a method, while efficacy refers to how well a pregnancy is prevented with the perfect use of a method (52). Many of the non-barrier contraceptive methods have similar efficacy; but, because of the varying degree of user involvement with each method, the effectiveness differs significantly between non-barrier contraceptive options (52). LARC and sterilization require no user involvement; and, proper and consistent use is essentially guaranteed. These methods have nearly identical efficacy and effectiveness. However, methods such as the pill, the injectable, and the condom require different degrees of user involvement, and allow for potential imperfect use. This potential user error results in reduced effectiveness compared to reported efficacy.

The Pearl Index is used to compare the effectiveness of different birth control methods and represents the number of contraceptive failures per 100 women-years of use (52). The most effective form of birth control is the hormonal subdermal implant. The Pearl Index of the ENG implant reported from the Trussell study is 0.05 (52). However, subsequent studies reported that the implant may have a higher effectiveness. A study of 24,100 cycles in 923 women suggests that the Pearl Index of the subdermal implant is 0.006 (53). Pearl Indices for LARC methods available in the United States are listed in *Table 3* (20,52,54,55). A study of 61,488 women from 2006-2012 suggests that the Pearl Indices of LNG-IUDs and copper IUDs may be lower than typically quoted with a Pearl Index of collective LNG-IUDs of 0.06 (95% CI: 0.04–0.09) and a Pearl Index of copper IUDs of 0.52 (95% CI: 0.42–0.64) (56).

When the Pearl Indices are compared, there is no significant difference in pregnancy rates over time between different LNG-IUDs (20). It has also been shown that different LNG-IUDs are similarly effective regardless of age, parity, and BMI (55). Studies have also shown that the LNG subdermal implant is effective in overweight and obese women (57). Based on data collected from the National Survey of Family Growth from 2006-2010, LARC had the lowest failure rates of all contraceptive methods, with a combined failure rate of 1% (3).

Safety of LARC methods

Overall, studies continue to show that the ENG subdermal

Table 4 Contraindications to use of LARC methods (8,58,59)

ENG subdermal implant
Current pregnancy
Acute liver disease
Undiagnosed abnormal uterine bleeding
Breast cancer (current diagnosis or history)
Hypersensitivity reaction to components of the implant
LNG-IUD
Current pregnancy
PID within the last 3 months
Acute cervicitis
Post-partum or post-abortion sepsis within the last 3 months
Undiagnosed abnormal uterine bleeding
Genital tract malignancy
Uterine anomaly
Breast cancer (current diagnosis or history)
Copper IUD
Current pregnancy
PID within the last 3 months
Acute cervicitis
Post-partum or post-abortion sepsis within the last 3 months
Undiagnosed abnormal uterine bleeding
Genital tract malignancy
Uterine anomaly
Wilson's disease

LARC, long-acting reversible contraceptive; LNG-IUD, levonorgestrel intrauterine device; ENG, etonogestrel; PID, pelvic inflammatory disease.

implant, the LNG-IUD, and the copper IUD are safe for use in adolescent and young adult women, including nulliparous women. The US Medical Eligibility Criteria for Contraceptive Use categorizes ENG subdermal implant as safe for nulliparous women to use without restrictions (8,58). It categorizes use of both the LNG-IUD and the copper IUD in nulliparous women as having advantages that outweigh theoretical or proven risks (8,58). Contraindications to the use of each method are listed in *Table 4* (8,58,59). Major safety concerns regarding LARC pertain almost exclusively to IUDs and include: device expulsion, uterine perforation, pelvic inflammatory disease (PID), ectopic pregnancy, and infertility after discontinuation of the method.

Table 5 Rate of uterine expulsion of IUDs (20,54,55,60-65)

IUD[1]	Rate of uterine expulsion, %
LNG-52 mg (Mirena)	1.6 (65)
LNG-19.5 mg (Kyleena)	3.6 (20,55)
LNG-52 mg (Liletta)	3.5 (54)
LNG-13.5 mg (Skyla)	4.6 (20,55)
Copper T380A (ParaGard)	4.9 (65)

[1], US brands: Kyleena, Mirena, and Skyla, manufactured by Bayer HealthCare Pharmaceuticals, Ind, Whippany, USA. Liletta, manufactured by Allergan, Irvine, California, USA. Paragard manufactured by CooperSurgical Inc., Trumbull, CT, USA. IUD, intrauterine device; LNG, levonorgestrel.

IUD expulsion is rare and occurs at similar rates regardless of IUD type (*Table 5*) (20,54,55,60-65). IUD expulsion is not technically a safety issue, but it does increase the risk of unintended pregnancy (60). One study found that the odds ratio of increased IUD failure with IUD expulsion was 3.31 (95% CI: 1.40–7.81) (61). While the rates of uterine expulsion between nulliparous and parous women using the LNG-IUD were similar, rates of uterine expulsion were slightly higher for nulliparous women compared to parous women using the copper IUD (62). There is an increased risk of expulsion of the copper IUD if it is reinserted after an expulsion (63). The rate of expulsion increases if the first expulsion occurs within the first three months after IUD placement (41% *vs.* 18%, P=0.001) (63). Risk of copper IUD expulsion decreases with age (60). Expulsion was more likely to occur in parous compared to nulliparous women with LNG 19.5 and LNG-52 (55,64). Expulsion of LNG-52 was not affected by parity (65).

Uterine perforation by LNG-IUDs and copper IUDs is rare. Multiple studies show uterine perforation affects between 0-1.3percent of women using IUDs (60,65-67). Perforation is most likely to occur during insertion of the IUD. A study of 61,448 women from 2006 to 2013 found uterine perforation occurred with 1.4 per 1000 insertions of the LNG-IUD (95% CI: 1.1–1.8) (68). It found that uterine perforation occurred in 1.1 per 1,000 insertions of the copper IUD. (95% CI: 0.7–1.7) (68).

Pelvic inflammatory disease (PID) as a result of an IUD use is rare, with rates ranging from 0–2.5% (65,69-71). This rate is comparable to the rate of PID found with the use of ENG implant, oral contraceptive pill, and depo-

medroxyprogesterone injection (60,72). There is an increased risk of PID during the first 20 days after insertion of an IUD if a chlamydia or gonorrhea infection is present at the time of insertion (73). This is thought to be due to the entrance of existing vaginal bacteria into the uterus via direct contact with the IUD during insertion (73). PID risk is not increased in nulliparous women (62). A randomized trial of 2,500 women found that LNG-IUD significantly lowered the risk of PID compared to the copper IUD and non-IUD users (62,74). It also found PID rates to be comparable in copper IUD and non-IUD users (62,74). The protective effects of the LNG-IUD could be explained by the endometrial suppression and cervical mucus thickening that is responsible for the method's contraceptive effects (74).

While the relative risk of ectopic pregnancy increases with IUD use, the absolute risk decreases due to the effectiveness of IUDs at preventing pregnancy (65-66,70,75,76). A study of 61,448 women from 2006 to 2012 calculated the risk of ectopic pregnancy to be 0.06 per 100 women-years (95% CI: 0.04–0.09) for the LNG-IUD, and 0.52 per 100 women-years (95% CI: 0.42–0.64) for the cooper IUD (56). Absolute ectopic pregnancy risk is lower with the LNG-IUD compared to the copper IUD. The hazard ratio for ectopic pregnancies with LNG-IUD and copper IUD use is 0.26 (95% CI: 0.10–0.66) (56).

Fertility returns rapidly after implant and IUD removal (62,70,77-80). Studies have found no overall difference in 12-month pregnancy rates with IUD users compared to non-IUD users after removal of the IUD (81). The copper IUD is not a risk factor for tubal occlusion leading to infertility (82).

Studies suggest that the ENG implant, LNG-IUD, and copper IUD do not negatively affect bone mineral density and can be safely used in adolescents who have not reached peak bone mass (83-85). LNG-IUD use may be associated with reduced fracture risk (86).

A change in menstrual pattern and irregular menstrual periods are a common concern, especially during the first year of ENG subdermal implant use (86,87). Other side effects associated with the use of ENG subdermal implant include headache, weight gain, acne, dizziness, depressed mood, nausea, lower abdominal pain, hair loss, loss of libido, and an increased risk for the development of ovarian follicular cysts (86,87). Rare safety concerns are associated with the procedure of insertion and removal of the implant. In general, subdermal implant is well accepted and most side effects are infrequent and rarely require discontinuation or removal of the device (86,87).

Use of LARC methods by adolescents

Data from 2015 suggests that only 3.4% of adolescents in the United States use a LARC method (95% CI: 2.9–3.9) (88). This study found that older adolescents are more likely to use LARC than younger adolescents, with an adjusted odds ratio of 2.41 (95% CI: 1.62–3.58) comparing 20–21 and 15–17 years old (88). A number of factors have been identified as barriers (*Table 6*) or facilitators (*Table 7*) for

Table 6 Barriers to LARC method use by adolescents (64,71,88-99)

Domain	Barriers
Medical practitioner factors	Perception that LARC not appropriate for adolescents
	LARC not offered due to safety concerns
	Belief that IUDs should not be used in nulliparous females
	Previous STI and multiple sex partners incorrectly considered as contraindication
	Perception that adolescents not interested in LARC
	Lack of training for LARC placement
	Lack of confidence in ability to adequately counsel regarding LARC
	Belief that LARC methods are traumatic to adolescents
	Do not feel that they can keep up with clinical skills needed for LARC use
Adolescent factors	Not offered LARC option or counselled by their physician
	Fear of complications with IUD placement and use
	Fear of pain with insertion or removal of IUD or implant
	Fear of limitation of physical activity with IUD use
	Fear of expulsion of IUD, future infertility
	Fear of future fertility
	Concern about weight gain, and irregular bleeding
	Lack of anatomical knowledge to understand LARC and associated risks
	Misconception that LARC is not effective
	Concern about consent and confidentiality
	Belief that parental permission was needed for LARC placement
	Cost
	Concern that IUDs should not be used in nulliparous females

Table 6 (*continued*)

Table 6 (*continued*)

Domain	Barriers
System factors	Physician office not set up for LARC method placement
	Expense may not be covered by health system
	Insufficient access to physicians who will insert IUD or subdermal implant
	LARC method may not be readily available or in stock in the clinic or office
	Practice of requiring separate appointments for contraceptive counseling and LARC placement

LARC, long-acting reversible contraceptive; IUD, intrauterine device; STI, sexually transmitted infection.

Table 7 Facilitators for use of LARC method by adolescents (90,92,99)

Longer duration of method's effectiveness
Lack of user dependency with LARC methods
Increased knowledge regarding eligibility for LARC awareness efforts
Assurance of confidentiality
Elimination of cost barriers
Dispelling of misconceptions about risks and side effects
Acceptability and use by adolescent's social circle
Adolescent's personal acceptability of the method
History of prior pregnancy
Improved access

LARC, long-acting reversible contraceptive.

the adoption and use of a LARC method by adolescents (64,71,88-99).

Conclusions

LARC methods are the recommended methods of choice for contraception in adolescents and young adult women. The ENG subdermal implant, the LNG-IUD, and the copper IUD are safe and effective methods of contraception for adolescents and young adult women. The US Medical Eligibility Criteria for Contraceptive Use categorizes implant as safe for nulliparous women to use without restrictions. It categorizes use of both the LNG-IUD and the copper IUD in nulliparous women as having advantages that outweigh theoretical or proven risks. With appropriate education and training, medical practitioners in their primary care medical practice settings can effectively use LARC methods.

There needs to be better education and training for medical practitioners regarding the use of LARC methods including training in the proper procedures for insertion and removal of subdermal implant and IUDs. Training on LARC placement should be easily accessible to all medical practitioners who wish to make this a part of their practice. Additionally, adolescents and young adult women need education about LARC. Contraceptive counseling should include LARC methods, even if the adolescent did not request them. Medical practitioners should provide factual, non-biased information regarding all contraceptive methods, and use factors that the adolescent has identified as valuable in a birth control method to guide the discussion. Barriers associated with cost and confidentiality should be addressed at the policy level.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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