

Patient Acceptability, Safety and Efficacy of the Levonorgestrel-Releasing Intrauterine System (LNG-IUS)

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Abstract: The levonorgestrel-releasing intrauterine system (LNG-IUS) is a highly effective method of pregnancy prevention used by women throughout the world. Until recently, intrauterine contraception has been underutilized by US women particularly adolescents. This is primarily because of persistent misconceptions and myths held by clinicians and patients surrounding the safety and efficacy of these devices. This article presents the latest research regarding the acceptability, safety, and efficacy of the LNG-IUS.

Keywords: intrauterine contraception, adolescents, levonorgestrel, safety, efficacy, pregnancy prevention, long-acting reversible contraception, pelvic inflammatory disease



Introduction

Unintended pregnancy is a significant public health problem in the US. Though 90% of sexually active women use some method of contraception,¹ research suggests that nearly half of pregnancies are unintended.² Of these, 4 in 10 end in abortion.³ Women seeking to prevent pregnancy have a variety of contraceptive options with ranging efficacy rates and side effect profiles. However, the most commonly used method is the oral contraceptive pill.⁴ Because it requires daily adherence and monthly prescription refills, the typical use failure rate for oral contraceptive pills is relatively high (8% of women experience an unintended pregnancy within 1 year of use.⁵) The failure rates in adolescent users are even higher, ranging from 5%–25%, mainly due to non-compliance.^{6,7}

In recent decades more efficacious and long-acting, reversible contraceptive options have become available to women. Of these, intrauterine methods require minimal maintenance, offer very high efficacy rates, and are safe for most women.

Despite these benefits, both FDA approved intrauterine devices (IUDs), the copper and progestin-containing, are vastly underused by women in the US (1.9% of US women ages 15–44 rely on intrauterine contraception).⁸ In contrast, intrauterine contraception is the most commonly utilized method in the rest of the world.⁹

Intrauterine Contraception Options in the United States

Historical context

Intrauterine contraception was introduced in the United States in the mid-1960s. Because of strong efficacy data, IUDs were used by almost 10% of contraceptive users in the late 1970s.¹⁰ In 1971, the Dalkon Shield was FDA approved for use as a contraceptive and soon became the most popular IUD on the market.¹¹ Unbeknownst to providers and users, this device had a design flaw which led to increased risk of pelvic inflammatory disease,¹² tubal infertility¹³, and septic maternal death.¹⁴ As a result of ensuing lawsuits and patient distrust, IUD use fell dramatically. By 1988, only 2% of US women used IUDs for contraception and by 1995 this percentage had fallen to 0.2%.¹⁵

Though a multitude of studies attest to the safety of contemporary forms of intrauterine contraception, many providers maintain a level of concern in prescribing these methods.¹⁶

Intrauterine contraception options in the US

The levonorgestrel-releasing intrauterine system (LNG-IUS) is one of two intrauterine contraceptive methods available in the US. The Copper T 380 A (ParaGard[®], Duramed Pharmaceuticals, Cincinnati, Ohio) was introduced in the US in 1988 and is FDA approved for up to 10 years of use (though data indicate effectiveness up to 20 years¹⁷). Unlike the LNG-IUS, the copper IUD contains no hormones. By causing an increase in copper ions, enzymes, prostaglandins, and macrophages, the copper IUD impairs sperm function and therefore prevents fertilization.¹⁸ The copper IUD is extremely efficacious: data indicate that the cumulative 12-year failure rate is 2.2 pregnancies per 100 women.¹⁹ The copper IUD can also be used as a form of emergency contraception. When inserted within 5 days of unprotected intercourse, it has a failure rate of 1%.^{20,21}

The LNG-IUS was FDA approved in 2000 but was not available for commercial use until 2001. It consists of a polyethylene T-frame surrounded by a cylinder containing 52 mg of levonorgestrel, a potent 19-nortestosterone derivative, in polydimethylsiloxane attached to the vertical stem. Though FDA approved for 5 years, clinical trials indicate high levels of effectiveness for at least 7 years.²²

Initially after insertion, 20 mcg of levonorgestrel is released daily into the uterine cavity. After 5 years, this rate declines to 14 mcg per day. The LNG-IUS prevents pregnancy by exposing the uterus to high local levels of levonorgestrel while minimizing systemic hormone levels.²³ Specifically, the LNG-IUS exerts its contraceptive effect by thickening cervical mucus to reduce sperm penetration, inhibiting sperm motility and function, and causing endometrial atrophy. The system suppresses ovulation in only 25% to 50% of users.²⁴ Because this method requires very minimal maintenance, perfect and typical use failure rates for the LNG-IUS are identical (0.2 per 100 women),²⁵ rivaling those of permanent surgical sterilization among women under the age of 26 years.



Safety and Side Effects

Insertion

Unlike most other methods of contraception, both forms of intrauterine contraception require professional insertion. Patients should be advised that discomfort during the insertion process is common and may be followed by 10–15 minutes of cramping pain. Some providers give non-steroidal anti-inflammatory drugs in advance of insertion but a recent study of first-time IUD users indicated that 400 mg of ibuprofen given 45 minutes before the procedure had no significant impact on reducing pain compared to placebo.²⁶ An older, smaller study found that administration of 2% intracervical lignocaine gel may alleviate insertion discomfort in some users.²⁷ Anecdotally, some gynecologists recommend administering a paracervical block with lidocaine prior to placement of the tenaculum, sounding and IUD insertion either with or without pre-treatment with misoprostol (buccally or vaginally) to soften and dilate the cervix.

Importantly, in a recent study,²⁸ 95% of participants (n = 506) had successful insertions of the LNG IUS at first attempt, and less than 1% were unsuccessful after two attempts. Additionally, insertion process was described as “easy” by 92% of the investigators.

Perforation

Uterine perforation is very small possibility during insertion is rare. Research indicates that when inserted by an experienced provider, risk of perforation is 1 per 1000,²⁹ underscoring the need for adequate provider training in the correct insertion process.

Risk for pelvic inflammatory disease

Research indicates having an IUD in place does not increase risk of pelvic inflammatory disease (PID).³⁰ It is the insertion process, not the usage of the device nor the strings, that can increase risk of infection.^{31,32} To prevent introducing sexually transmitted diseases (STDs) into the uterus, many clinicians routinely screen for STDs prior to inserting an IUD, especially in high risk populations such as adolescents. In addition to reduce the risk of infection, the vagina is usually prepped with betadine or another antimicrobial solution and the IUD is inserted using sterile technique. Additionally, a randomized controlled trial and cohort studies have demonstrated that the

monofilament string does not increase the risk of infection.³³ Large international trials conducted by the World Health Organization concluded that infection risk was limited to the first 20 days after insertion. This risk falls and remains steady in subsequent years.³⁴ Because of the risk of infection after insertion, some providers have considered administering a prophylactic antibiotic to reduce insertion complications. However, a Cochrane Review performed to assess the effectiveness of this practice showed little effect on PID occurrence and therefore, is not recommended in low risk populations.³⁵ In settings with a high prevalence of STDs, prophylaxis has been shown to reduce the risk of salpingitis by about a third.³⁶ Unlike the other forms of intrauterine contraception, the LNG-IUS may actually lower the risk of PID, although data are inconsistent.^{37,38} Impenetrable cervical mucus, endometrial thinning, and reduced retrograde menstruation may lead to a possible protective effect.³⁹ Should PID occur related to the IUD insertion process or later, the IUD should be left in place during antimicrobial treatment for PID; removal of the IUD should only be considered after failure of a routine course of PID treatment.

Tubal infertility

There is also widespread confusion regarding the risk that intrauterine contraception methods pose to future fertility. There is no evidence that use of intrauterine contraception causes an increase in tubal infertility.^{40,41} Additionally, despite endometrial suppression during LNG-IUS use, fertility is unaffected after removal. In a European randomized multicenter study,⁴² researchers found that the cumulative conception gross rate after removal was 79.1 per 100 (86.6 after 24 months). These results suggest that the endometrium recovers quickly and normal ovulation is established after discontinuation of use.

Sexually transmitted infection risk

Research does not support routine screening for STDs in low-risk women (over 25 years of age, in low prevalence populations, etc.) before IUD insertion. However, women at high risk for chlamydia and gonorrhea may benefit from screening. In the case of a positive test, the American College of Obstetricians and Gynecologists recommends that “clinical judgment should be used to determine whether the



IUD should be removed.”⁴³ Most family planning experts would not advise removal of the IUD. If an STD test is positive at the time of screening, it is recommended to treat the infection and the IUD may be inserted 1 week after treatment is completed.

Foreign body reaction

All forms of intrauterine contraception induce a local inflammatory reaction of the endometrium whose cellular and humoral components are expressed in the tissue and the fluid filling the uterine cavity.⁴⁴ Nevertheless, this is not the IUDs primary mechanism of action for preventing pregnancy and the local inflammatory reaction does not cause long term negative effects on the endometrium.

Expulsion

Approximately 2%–8%^{45,46} of users of intrauterine contraception experience device expulsion. This most often occurs during the first 3 months after insertion.⁴⁷ The risk of expulsion does not seem to be increased in nulliparous women.⁴⁸ In general, expulsion risk is about 1% per year of IUD use. About 1 expulsion in every 5 goes unnoticed at the time.⁴⁹ This can increase the risk of unintended pregnancy as the pregnancy rate in women who have experienced an expulsion is 1 in 20.⁵⁰

Progestin-related side effects

Because a small amount of levonorgestrel is absorbed systemically, some progestin-related side effects can but rarely do occur. However, women using the LNG-IUS receive 10% of the dose of daily hormones as those taking a combined oral contraceptive pill containing 150 mcg levonorgestrel.⁴⁹ Additionally, the mean concentrations of levonorgestrel for the LNG-IUS are lower than with oral contraceptive pills (both combined and progestin-only) and subdermal implants.⁵¹ As with all forms of progestin-only contraception, the LNG-IUS is associated with initial menstrual irregularities. Women often experience frequent bleeding/spotting for the first 3 months after insertion.⁵² Within 6 months, most women experience markedly reduced bleeding and about 20% of women will have amenorrhea after 12 months of LNG-IUS use.⁵³

Bleeding and pain are the main reasons that users give for removing their IUDs prematurely. Therefore, discussing these side effects, how the patient will

tolerate changes in bleeding, and proper management is essential. A recent Cochrane Review⁵⁴ examined the use of nonsteroidal anti-inflammatory drugs to alleviate these symptoms. Fifteen randomized studies and more than 2700 women were assessed and results revealed that these drugs (including naproxen, suprofen, mefenamic acid, ibuprofen, indomethacin, flufenamic acid, alclofenac and diclofenac) all equally reduced bleeding and pain. Based on these results, the authors asserted that nonsteroidal anti-inflammatory drugs should be used to treat bleeding and pain associated with IUD use.

Benefits

The LNG-IUS has many characteristics that make it appealing to women. It is highly effective, allows privacy, does not require action at the time of intercourse nor partner cooperation, and does not necessitate short-interval pharmacy or clinic visits. Additionally, the LNG-IUS has been shown to be the most cost effective reversible method of contraception after 5 years of continuous use.⁵⁵ However, in 2010, the price of the LNG-IUS increased 30%. This increase may affect LNG-IUS' cost effectiveness when compared with other methods.⁵⁶

Menstrual-related benefits

In addition to these factors, the LNG-IUS has several non-contraceptive benefits. Primarily, the LNG-IUS can improve menstrual-related side effects including dysmenorrhea, menorrhagia and endometriosis. In fact, in 2009, the FDA approved the LNG-IUS for treatment of heavy menstrual bleeding.⁵⁷

The LNG-IUS has been shown to be very effective in reducing pain in women who experience dysmenorrhea, a common condition mainly affecting younger women. In one study of LNG-IUS users, the prevalence of menstrual pain decreased from 60% before insertion of the LNG-IUS to 29% within 3 years after insertion.⁵⁸

Research also indicates that the LNG-IUS is an excellent treatment for menorrhagia, a disorder affecting 2.5 million women in the US. Menorrhagia is defined as a loss of 80 ml or more of menstrual blood per month or bleeding for more than 7 days. Treatment with the LNG-IUS has been shown to reduce menstrual blood flow by 86%–97%.⁵⁹ A meta-analysis of several randomized controlled trials demonstrated that the LNG-IUS is more effective than cyclical norethindrone in treatment



of menorrhagia.⁶⁰ Research also suggests that the LNG-IUS may be an acceptable alternative to hysterectomy in women with menorrhagia.⁶¹ Additionally, the LNG-IUS has been successfully used to treat women with Von Willebrand disease-related menorrhagia. In a recent study of women with Von Willebrand disease, participants had at least 1 day a month when their lives were severely affected by bleeding, and 37.5% had at least 3 affected days per month. Nine months after insertion of the LNG-IUS, none of them had any days of the month that were severely affected by menstruation and relief persisted through 53 months.⁶² Subsequent studies have also had positive results.⁶³

Endometriosis affects 5%–10% of women of reproductive age women in the US and is associated with chronic pelvic pain, dyspareunia and infertility.⁶⁴ Several small clinical trials have investigated the effectiveness of the LNG-IUS for the treatment of endometriosis. The results demonstrate that the LNG-IUS reduces menstrually-related pain over 3 years, with most of the improvement being in the first 12–18 months.^{65–67} One trial compared use of the LNG-IUS with a GnRH agonist, depot leuprolide 3.75 mg given intramuscularly every 28 days. Results demonstrated that both treatments were equally effective in relieving endometriosis pain over a 6 month treatment but the LNG-IUS users had the additional benefits of fewer hypoestrogenic side effects such as hot flashes, vaginal dryness, decreased libido, mood swings, headache, and bone mineral density depletion, and only requires one intervention every 5 years.⁶⁸

Ectopic pregnancy

Until recently, history of ectopic pregnancy has been a contraindication for IUD use. However, a meta-analysis of 16 case-controlled studies concluded that intrauterine contraception does not increase ectopic pregnancy risk. In fact, rates of ectopic pregnancy in the LNG-IUS users are lower because it is such an efficacious method of pregnancy prevention.⁶⁹ Prospective data from a randomized controlled trial indicate that the risk of ectopic pregnancy associated with LNG-IUS use is 0–0.5 per 1000 woman years compared with 3.25–5.25 per 1,000 woman-years in women who do not use contraception.⁷⁰ However, if pregnancy does occur with an IUD in place, there is an increased risk of it being an ectopic pregnancy compared to non-users.

Endometrial cancer

Because the LNG-IUS delivers hormones locally, it should provide protective effect against endometrial cancer^{71,72} A small study was conducted to evaluate the use of the LNG-IUS to treat non-atypical and atypical endometrial hyperplasia in women. Based on the results, researchers concluded that the LNG-IUS is a promising alternative to hysterectomy for the treatment of endometrial hyperplasia and could enhance the success rate when compared with other routes of progestin administration.⁷³

A larger long-term, prospective study evaluated 3 treatment options for endometrial hyperplasia, comparing effects of LNG-IUS, low oral dose of medroxyprogesterone acetate (MPA) and no treatment (observation only). Results indicated that 6 months treatment with LNG-IUS proved significantly superior to the other 2 groups. LNG-IUS was also significantly superior at 58 to 106 months.⁷⁴

Endometrial suppression during hormonal suppression use

Several studies have been conducted assessing the LNG-IUS to protect the endometrium from endometrial hyperplasia or malignant transformation during exogenous estrogen replacement therapy in perimenopausal and postmenopausal women. A systematic overview of the literature revealed that endometrial suppression and symptomatic improvement of menopausal symptoms was achieved in all LNG-IUS users in these studies.⁷⁵ One study comparing continuous oral estrogen and levonorgestrel with continuous oral estrogen and the LNG-IUS indicated that though both groups experienced symptom improvement, the women in the LNG-IUS were amenorrhoeic while the other group continued with cyclic bleeding.⁷⁶

Patient Acceptability

Because of the contraceptive efficacy rates, ease of use, non-contraceptive benefits, the LNG-IUS is well tolerated by the majority of users. A 3 year study evaluating the long-term acceptability of the LNG-IUS in women 25–45 years of age indicated that percentage of women who were “very satisfied” with the method increased steadily with the duration of use (29% after two weeks, 56% after 2 months, 69% after six months and 77% after 36 months).⁷⁷ A later study of women 18–45 years of age revealed that 84.5% of users



indicated a high level of satisfaction with the LNG-IUS at 12 months.⁷⁸ A smaller study evaluating patient satisfaction with the LNG-IUS found that although 12% of users had the device prematurely removed (major reasons for removal were heavy bleeding and pain), the majority of participants were satisfied with their results: 72% of the women reported they would use the LNG-IUS again, 73% would recommend it to their peers, and the overall satisfaction rate was 76%.⁷⁹ One-year continuation rates for the LNG IUS and the copper-containing IUD are 81% and 78%⁸⁰ respectively.

Counseling

As with any form of contraception, candidates for the LNG-IUS should be counseled regarding the risks and benefits of the method. Research indicates that patient satisfaction correlates to the amount of information the patient received about possible side effects. This held true whether or not the patient actually experienced that specific symptom.⁸¹

Condoms or abstinence may need to be advised for 7 days after inserting the LNG-IUS unless the current contraceptive method is still effective or insertion occurred within the first 7 days of the cycle.⁸² It is also important to counsel women switching from a hormonal method like the pill, patch, or ring to the LNG-IUS, that bleeding is likely to occur upon discontinuation of the combination method for 7 days after LNG-IUS insertion. Like all other contraceptive methods, the LNG-IUS does not protect against STDs so patients should be advised to use condoms and should get STD screening per routine annual guidelines for those age 25 years and younger or per sexual history, symptoms, etc.

To help facilitate use, providers should give each woman an identification card with the name and picture of the device, date of insertion, and date of removal. Additionally, patients should be given instructions for checking the strings and what to do in the event that the device comes out. Some clinicians advise against women routinely checking their IUD strings, even after menses, because this can lead to unnecessary anxiety since many women cannot feel their IUD strings or may accidentally pull on the strings and dislodge the IUD.

Candidates for Use of the LNG-IUS⁸³

- Multiparous and nulliparous women desiring longer term, highly effective, reversible contraception

- Women with contraindications to estrogen
- Women with the following medical conditions for which an intrauterine device may be an optimal method:
 - Thromboembolism⁸⁴
 - Menorrhagia/dysmenorrhea⁸⁵

Contraindications for IUD Insertion^{86–89}

- Pregnancy
- Pelvic inflammatory disease (current or within the past 3 months)
- Current STD
- Puerperal or post-abortion sepsis (current or within the past 3 months)
- Purulent cervicitis
- Undiagnosed abnormal vaginal bleeding
- Malignancy of the genital tract
- Known congenital or acquired uterine anomalies or fibroids distorting the cavity in a way incompatible with intrauterine device insertion
- Allergy to any component of the IUD

Special Populations

Adolescents

The US has one of the highest teenage pregnancy rates in the industrialized world.⁹⁰ Currently, 750 000 teenagers become pregnant is there twice,⁹¹ and 82% of these pregnancies are unintended. Between 2005 and 2006, the teen pregnancy rate increased for the first time in more than a decade, rising 3%.⁹² Despite this recent rise, there have been significant declines in teenage pregnancy rates in the past 2 decades. Research reveals that contraception has played a significant role in this decline: a 2007 study showed that 86% of the decline in teenage pregnancies was primarily a result of improved contraceptive use.⁹³

Although a certain level of controversy still exists regarding the use of intrauterine contraception in adolescents, the World Health Organization⁹⁴ and the American College of Obstetricians and Gynecologists⁹⁵ support its use in this population asserting that the benefits generally outweigh the risks. The American Academy of Pediatrics stipulates that intrauterine contraception may be appropriate for adolescents who have children and are protecting themselves from STDs.⁹⁶

There are some important considerations for providers considering providing the LNG-IUS to



adolescents. Mainly, adolescents are more likely than adult women to discontinue use of any contraceptive method. This is also the case with LNG-IUS users. Adolescent discontinuation rates at 12 months are slightly higher than adult women.⁹⁷ In 2 studies, the continuation rates at 12 months ranged from 48%⁹⁸ to 88%.⁹⁹ However, a recent randomized controlled trial demonstrates that women 18–25 years of age are more likely to continue using the LNG-IUS at 1 year compared to those using the pill (80% vs. 73%).¹⁰⁰

As previously mentioned, discomfort and cramping is common during insertion, particularly among nulliparous adolescents. In one study, 86% of adolescents reported mild to severe pain with insertion.¹⁰¹ There is some evidence that misoprostol administration prior to insertion may soften and dilate a nulliparous cervix.¹⁰² Additional pain relieving techniques have been discussed earlier in the paper.

Some studies indicate a higher expulsion rate in adolescent women, particularly those who are nulliparous, although rates vary widely (5%–22%).^{103–106}

Because this population is at high risk for acquiring STDs, all adolescents should be screened for chlamydia and gonorrhea prior to insertion.^{107,108} In the case of a positive test, patients should be treated promptly and the IUD may be inserted 1 week after treatment is completed. The research regarding adolescent use of intrauterine contraception is scant, necessitating further study in this area. However, intrauterine contraception presents a tremendous opportunity to decrease rates of unintended pregnancy among adolescents. With sufficient counseling on the risks and benefits as well as the importance of dual condom and contraceptive use, adolescents make ideal candidates for the LNG-IUS.

Conclusion

The levonorgestrel-releasing intrauterine system is a highly effective, safe, affordable, and low maintenance method of long-acting, reversible contraception. Although misconceptions persist regarding the risks associated with use, a full body of research attests to the method's efficacy, safety and benefits. Although initial minor side effects are common, these tend to alleviate over time and users generally report high rates of satisfaction with the method. The LNG-IUS, therefore, is an excellent choice of contraception for most women, including adolescents and those who are nulliparous.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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