

Essential Knowledge about the LNG-IUS

This document provides an overview of key biomedical, social science, and programmatic knowledge about the LNG-IUS, the levonorgestrel-releasing intrauterine system, as of January 2009. For information about Mirena®, the commercially-marketed LNG-IUS, visit <http://www.bayerhealthcare.com>. For detailed information about the Copper-T 380 IUD, see the “[Essential Knowledge](#)” section of the IUD Toolkit, and the “[Hormonal IUD](#)” section for more information about the LNG-IUS.

I. Method Characteristics of the LNG-IUS

Hormone-Releasing System

The T-shaped LNG-IUS releases 20 µg daily of levonorgestrel (the progestin widely used in implants and oral contraceptive pills) directly into the uterine cavity. This ensures high hormonal concentration in the endometrium and adjacent tissues and low hormonal levels in the blood stream. Thus, systemic side effects are minimized. Plasma levels of levonorgestrel with the LNG-IUS are lower than those seen with subcutaneous implants, combined oral contraceptives, and progestin-only pills (Jensen, 2005; Sturridge and Guillebaud, 1996).

Effectiveness

The LNG-IUS, like the copper-bearing TCu-380A, is a highly effective form of long-acting, reversible contraception. A review of studies conducted over the past 20 years showed that the LNG-IUS has a five-year cumulative pregnancy rate of < 0.5 percent. This means that over 5 years of use of the LNG-IUS, only 5 women out of 1,000 will become pregnant (Thonneau and Almont, 2008).

Return to Fertility

After removal of the LNG-IUS, there is no delay in a woman's return to fertility (Andersson et al., 1992; WHO, 2007; Skjeldestad, 2008).

Lifespan after Insertion of LNG-IUS

The LNG-IUS is effective for up to five years after insertion (Jensen, 2005); some evidence suggests that it may be effective for up to seven years (Sivin et al., 1991). In the

United States, the Food and Drug Administration has labeled the LNG-IUS, commercially marketed as Mirena[®], as effective for five years (USFDA, 2008).

Mechanism of Action

Levonorgestrel released by the LNG-IUS into the uterine cavity has several local effects, including thickening of the cervical mucus and inhibiting sperm movement. It also suppresses the growth of the endometrium. In addition, the LNG-IUS, like copper-bearing IUDs, creates a foreign-body reaction in the uterine cavity that hinders sperm and ovum transport, which prevents fertilization. In all cases, the LNG-IUS prevents pregnancy prior to implantation (Jensen, 2005).

Side Effects

Menstrual changes

Use of the LNG-IUS may be associated with bleeding irregularities that tend to stabilize within 3 to 6 months after insertion (Andersson et al., 1994; Mansour, 2007; Ibraheim et al., 2005). Long-term use of the LNG-IUS often leads to decreased menstrual bleeding, oligomenorrhea (infrequent bleeding), or amenorrhea (absence of bleeding) (Diaz et al., 2000; Grimes et al., 2007). Approximately 17 percent of women will experience amenorrhea at 1 year after insertion, and as many as 60 percent will be amenorrheic with long-term use (Mansour, 2007). All bleeding irregularities are reversible and do not negatively impact users' health (Zhang, 2001).

Systemic hormonal side effects

Because systemic absorption of the levonorgestrel released by the LNG-IUS is low, hormonal side effects are less pronounced than with many other hormonal methods. These side effects are often transient and include acne, headache, mood disturbance, dizziness, breast sensitivity, nausea, and fluid retention (Mansour, 2007; WHO, 2007). Only 1 percent to 2 percent of women discontinue use of the LNG-IUS because of systemic side effects (Mansour, 2007). A small number of LNG-IUS users will develop simple ovarian cysts because plasma levonorgestrel levels disrupt ovulation in some cycles and cause enlarged follicles (Bayer, Inc., 2008). These cysts can cause pelvic pain, but in most women they are asymptomatic and do not require any treatment; 94 percent of cases resolve spontaneously within 6 months (Inki, 2002; Mansour, 2007).

Non-Contraceptive Health Benefits

It is well documented that the LNG-IUS is an effective treatment option for women suffering from idiopathic menorrhagia (heavy, prolonged menstrual bleeding) (Andersson et al., 1990; Xiao et al., 2003; Kriplani et al., 2007). Idiopathic menorrhagia occurs in 20 percent to 30 percent of women of reproductive age and can cause or worsen anemia, particularly among women in developing countries where iron deficiencies are common. The LNG-IUS is an attractive treatment alternative to hysterectomy (surgical removal of the uterus), especially for women who cannot access surgical care or who are interested in preserving their fertility (Barrington and Bowen-Simpkins, 1997; Hurskainen, 2004; Kriplani et al., 2007). It is also comparable to other minimally invasive methods of treatment of excessive bleeding (Jensen, 2002), and it is medically superior to a regimen of oral progestins (Grimes et al., 2007). Cost-effectiveness analysis reveals that indirect

and direct costs of using the LNG-IUS to treat menorrhagia are substantially less than those for hysterectomy (Hurskainen, 2004). A study in India demonstrated that in addition to being an effective method of treatment, the LNG-IUS was well accepted by patients for the management of menorrhagia (Kriplani et al., 2007).

In addition, the LNG-IUS has been used for the treatment of endometriosis (a condition that occurs when functioning endometrial tissue grows in places other than the uterus which may result in severe abdominal discomfort and painful, excessive menstrual bleeding), adenomyosis (a condition that occurs when endometrial tissue is found within the muscular layer of the uterus), and dysmenorrhea (painful menses), and for endometrial protection during estrogen replacement therapy (Jensen, 2002; Jensen, 2005; Mansour et al, 2007). Preliminary evidence also suggests that the LNG-IUS may be used to treat menorrhagia associated with uterine fibroids and endometrial hyperplasia (excessive growth of the endometrium) (Varma et al., 2006).

Perforation

Perforation of the uterus during insertion is very rare. In a large observational cohort study, the rate of perforation was 0.9 per 1,000 insertions (FFPRHC, 2004). The skill and experience of the provider is the most important factor that minimizes the risk of perforation (Harrison-Woolrych et al., 2003).

Expulsion

Expulsion of the LNG-IUS is uncommon. Over 5 years of use, spontaneous expulsion will occur in approximately 5 percent of users (Mansour, 2007). In a recent review, the LNG-IUS was associated with a slightly higher rate of spontaneous expulsions than were copper IUDs with >250 mm² copper surface area, such as the TCu-380A (Grimes et al., 2007). Expulsion rates with the LNG-IUS do not vary by parity (Prager and Darney, 2007).

Ectopic Pregnancy

Because it is so effective in preventing pregnancy, the LNG-IUS protects well against ectopic pregnancy. In the unlikely event that a woman with the LNG-IUS becomes pregnant, the chance of that pregnancy being ectopic is increased. However, because pregnancies are so rare among LNG-IUS users, the absolute number of ectopic pregnancies is still much smaller than among women who use no contraception. Data from prospective, randomized clinical trials reveal that the 5-year cumulative rate of ectopic pregnancy ranges from 0.06 to 0.5 per 100 women with use of the LNG-IUS. In a cross-sectional survey study, the rates of ectopic pregnancies were 0.045 and 0.22 per 100 women at 1 and 5 years respectively (Backman et al., 2004). These rates are lower than the estimated rate of ectopic pregnancy of approximately 2 per 100 women of reproductive age in the general population (Murray et al., 2005). Use of the LNG-IUS is not contraindicated for women who have had an ectopic pregnancy in the past (WHO, 2004a). Despite the low risk in LNG-IUS users, ectopic pregnancy is a serious and life-threatening event, so providers must be aware of its signs and symptoms.

STI-Related Health Risks

Pelvic inflammatory disease (PID)

Rates of PID are very low among LNG-IUS users. In one study, the cumulative 36-month rate of PID was 0.5 among LNG-IUS users (compared with 2.0 in copper Nova-T users) (Toivonen et al., 1991).

Researchers have found that an increased risk of PID exists within the first 20 days after insertion of *copper* IUDs (Prager and Darney, 2007; FFPRHC, 2004). PID in IUD users is usually caused by (recognized or unrecognized) sexually transmitted infections (STIs) when the organisms *chlamydia trachomatis* or *gonococcus* are spread during the insertion from the cervical canal to the upper reproductive tract. PID is not caused by the IUD itself (Grimes, 2000). After the first 20 days, PID is a very uncommon event (ACOG Committee, 2005). Although there are no comparable data for the LNG-IUS regarding the risk of PID following insertion, it is reasonable to expect that a similar increase in risk exists within the first 3 to 4 weeks of use if cervical infection is present. This is why the LNG-IUS should not be inserted if a woman has a current case of gonorrhea or chlamydia or if she might have been exposed to these STIs due to individual risk factors. After the first 3 to 4 weeks following insertion, PID risk in LNG-IUS users should be minimal. In fact, some preliminary physiologic and clinical evidence indicates that the LNG-IUS may actually help protect against PID (Prager and Darney, 2007; Toivonen et al., 1991; WHO, 2007).

Infertility

The use of the LNG-IUS does not increase the risk of infertility among parous or nulliparous women (Prager and Darney, 2007). In a study examining the relationships between infertility, IUD use, and sexually transmitted bacteria, the risk of infertility due to tubal damage was *not* associated with previous IUD use, but rather to past exposure to *chlamydia trachomatis* (Hubacher et al., 2001). Although this study addressed the relationship between use of *copper* IUDs and infertility, the findings can be extrapolated to use of the LNG-IUS. Moreover, the LNG-IUS may have a protective effect against PID, and thus, against tubal infertility (Prager and Darney, 2007).

A review of IUD studies found that pregnancy rates after IUD removal were similar to rates among the general population. While some data on LNG-IUS users were included in this review, the author acknowledges that further research is needed to address the question of whether LNG-IUS use impacts subsequent fertility (Skjeldestad, 2008).

HIV/AIDs

A recent study demonstrated that LNG-IUS use by women with HIV does not increase genital shedding of the virus. Among LNG-IUS users with HIV, bleeding patterns, ovarian function, and body iron stores are similar to those among users without HIV (Heikinheimo et al., 2006). For women with HIV who experience menorrhagia, the LNG-IUS may be used as an alternative to uterine surgery (Lehtovirta et al., 2007).

II. Client Attitudes and Behaviors Regarding the LNG-IUS

Satisfaction with the LNG-IUS

LNG-IUS users are highly satisfied with the method; continuation rates are 75 percent to 82 percent at 3 years (Mansour, 2007). Continuation rates are similar among users of the LNG-IUS, copper IUDs, and two-rod implants (Grimes et al., 2007). One study in the United States found that a vast majority of users rated their experience with the LNG-IUS as very positive and indicated that they liked the method much better than their previous form of contraception (Jensen, 2008).

Reasons for Discontinuation

Comparative studies have shown that LNG-IUS users are more likely to discontinue use because of amenorrhea, while users of the TCu-380A are more likely to discontinue use because of heavy bleeding and pain. The likelihood of discontinuing use because of amenorrhea increases over time with the LNG-IUS because women are more likely to develop amenorrhea the longer they use the method (French et al., 2001; French et al., 2000). Only 1 percent to 2 percent of women discontinue use because of systemic side effects (Mansour, 2007). Pre-insertion counseling about possible menstrual disturbance may decrease discontinuation rates of the LNG-IUS (Backman et al., 2002; Davie et al. 1996). (See Section III: Counseling.)

III. Service Delivery and the LNG-IUS

Who Can Use the LNG-IUS?

Almost all women can use the LNG-IUS, including young women (under 20 years old) and older women (over 40 years old), women who are postpartum or postabortion, nulliparous women, nulligravid women, women who have had an ectopic pregnancy or a previous case of PID, women with HIV, or women who have AIDS and are doing clinically well on antiretrovirals (WHO, 2004a).

In addition, the LNG-IUS can be used as a treatment option for patients with menorrhagia and possibly several other health conditions (see Section I: Non-Contraceptive Health Benefits).

There are only a few conditions for which WHO recommends that the LNG-IUS should not be used (WHO Medical Eligibility Criteria, Category 4), the common ones being pregnancy; postpartum or postabortion sepsis; and *current* purulent cervicitis, PID, or chlamydial or gonorrheal infection. Less common conditions for which the LNG-IUS should not be used include cervical, endometrial or breast cancer; distorted uterine cavity; pelvic tuberculosis; malignant trophoblastic disease; and unexplained vaginal bleeding believed to reflect a serious underlying condition. There are also a few conditions in which the LNG-IUS should not be inserted unless other methods are not available or not acceptable to the woman (Category 3). These conditions—all of which are rare in women of reproductive age—include acute deep venous thrombosis, certain types of liver tumors, and

severe cirrhosis. Not all of the conditions listed are contraindications for copper-containing IUDs; it is the hormonal content which makes the LNG-IUS inappropriate for patients with illnesses such as breast cancer and liver disease (WHO, 2004a).

Use of LNG-IUS by Women Who Are Breastfeeding

Use of the LNG-IUS by lactating mothers during the postpartum period does not negatively impact breastfeeding or the healthy development of breastfed babies (Shaamash, 2005). Levels of levonorgestrel in the breast milk of mothers using the LNG-IUS are extremely low (FFPRHC, 2004). WHO guidelines indicate that breastfeeding mothers can initiate use of the LNG-IUS starting as early as 4 weeks postpartum (WHO, 2008).

Use of LNG-IUS by Women at “Increased Risk” of STIs

The LNG-IUS can generally be inserted in women who might be judged as having an “increased risk” of STIs solely because of certain epidemiologic or socio-demographic characteristics (Category 2) (WHO, 2004a). Some examples of these characteristics include age (young), marital status (unmarried), level of education (low), or area of residence (e.g., a region where prevalence of STIs is high).

LNG-IUS insertion is not generally recommended if a woman has a high *individual* likelihood of exposure to chlamydia or gonorrhea (e.g., she or her partner has multiple partners), unless current gonorrhea and chlamydia (cervical infection) can be reliably ruled out prior to insertion. This is because the risks of initiating use in the presence of cervical infection (i.e., the risk of developing pelvic infection following insertion) will generally outweigh the benefits (Category 3). However, if a woman already has an LNG-IUS inserted and later becomes at higher risk of STI exposure, she can generally continue using the LNG-IUS (Category 2). (WHO, 2004a).

Use of LNG-IUS in the Presence of Chlamydia or Gonorrhea

The LNG-IUS should not be inserted in the presence of *current* purulent cervicitis, or chlamydial or gonorrheal infection (WHO, 2004a). If a woman who *already has an LNG-IUS in place* presents with current purulent cervicitis or chlamydial or gonorrheal infection, she should be treated for these STIs with appropriate antibiotics, but there is no need to remove the LNG-IUS (WHO, 2004a).

Use of LNG-IUS by Women with HIV-Infection

The LNG-IUS can generally be inserted and used by women at high risk of HIV or by HIV-infected women if other STIs, such as gonorrhea and chlamydia, can be reliably ruled out prior to insertion. The LNG-IUS can also be inserted in women with AIDS who are doing clinically well on antiretroviral (ARV) therapy. Women with AIDS should be closely monitored for signs of PID. Women with HIV who develop AIDS while using the

LNG-IUS do not have to have the LNG-IUS removed, even if they are not on ARV therapy (WHO, 2004a).

Counseling

Women who receive counseling at the time of insertion about possible side effects associated with the LNG-IUS have higher levels of user satisfaction, regardless of whether they subsequently experience those symptoms. The strongest association between increased user satisfaction and information received through advanced counseling exists when women were told about the possibility of decreased menstrual bleeding or amenorrhea due to the LNG-IUS (Backman et al., 2002; Davie et al., 1996). Health care providers should provide detailed information about possible side effects, especially about menstrual changes that patients could experience (Jensen, 2005).

Insertion Techniques

The insertion technique for the LNG-IUS is different from techniques required for the TCu-380A and other IUD devices and requires additional training. In a recent study, the majority of clinicians reported perceiving that insertion of the LNG-IUS was easier than insertion of the TCu-380A. Also, clinicians with no prior experience with the LNG-IUS were able to insert the device successfully 95 percent of the time after only 1 attempt; less than 1 percent were unsuccessful after 2 attempts. The study also showed that 68 percent of patients felt either no pain or mild pain during insertion (Jensen, 2008).

Timing of Insertion

The LNG-IUS can be inserted in the first 7 days of the menstrual cycle, or at any other time in the menstrual cycle, as long as the provider is reasonably sure that the client is not pregnant (WHO, 2004a). A pregnancy checklist based on criteria endorsed by WHO has been shown to be an effective tool for determining if a woman is not pregnant (Stanback et al., 1999).

A woman does not need to wait until she is menstruating to have the LNG-IUS inserted (WHO 2004b).

Postpartum Insertion

The LNG-IUS can be inserted any time within 48 hours after birth if a woman is not planning to breastfeed. (The provider must have special training in postpartum insertion of the LNG-IUS.) Women who are breastfeeding should not have an IUD inserted immediately postpartum due to concerns that the newborn liver is not mature enough to metabolize progestin ingested with breast milk. After 48 hours, regardless of breastfeeding status, it is recommended that insertion be delayed for at least 4 weeks postpartum, at which point the uterus returns to its normal size. Breastfeeding mothers can initiate use of the LNG-IUS starting at 4 weeks postpartum; after this point, use of the LNG-IUS will not negatively impact the healthy development of breastfed babies (WHO, 2008). There are no data on expulsion of the LNG-IUS following immediate postplacental insertion (within 10 minutes after removal of the placenta following childbirth) or early postpartum insertion (between 10 minutes and 48 hours after delivery). However, a 2003 review of articles on immediate postplacental insertion of the copper IUD indicates that

this approach is safe and effective, although spontaneous expulsion is more likely than with interval insertion (performed at least 4 weeks after delivery) (Grimes et al., 2003). Subsequent studies also demonstrated that expulsion rates were higher after both immediate postplacental and early postpartum insertion compared with insertion 6 weeks or more postpartum (Grimes et al., 2007; Eroglu et al., 2006; WHO, 2004a; WHO, 2008).

Postabortion Insertion

The LNG-IUS can also be safely inserted immediately after a first- or second-trimester abortion (spontaneous or induced) if no infection is present. Expulsion rates are higher when inserted immediately after a second-trimester abortion than following a first-trimester abortion (WHO, 2004a).

Cost Considerations

The LNG-IUS is not widely available in many developing countries because of its high cost (Mansour, 2007). Its commodity cost is significantly greater than the TCu-380A because no generic version is currently available. Therefore, the LNG-IUS may be most appropriate for women with concerns about excessive menstrual bleeding or pain (Grimes, 2007).

The price listed by the U.S. Agency for International Development (USAID) for the TCu-380A is US\$1.64, according to the 2007 International Drug Price Indicator Guide (MSH, 2007). USAID does not supply the LNG-IUS, so a comparable cost is not available. The manufacturer makes Mirena available at a public-sector price of US\$40 (Schwanenflugel, 2005). The International Contraceptive Access (ICA) Foundation provides some quantities of the product for free and at subsidized rates (see Section IV).

In the United States and other developed countries, IUDs—including the LNG-IUS—are the most cost-effective form of reversible contraception (Trussell et al., 2008; Trussell et al., 1995; Chiou et al., 2003; French et al., 2000).

IV. How Organizations and Providers Can Obtain the LNG-IUS

Free or subsidized supplies of the LNG-IUS can be obtained through the **ICA Foundation**, founded by the Population Council and Bayer Schering Pharma AG in 2003. The ICA Foundation donates the LNG-IUS to public organizations in developing countries, including NGOs, governments, and multilateral organizations. Donated supplies of the LNG-IUS are to be incorporated into local reproductive health services and distribution networks.

For more information, contact: ICA Foundation, PO Box 581, FI-20101 Turku, Finland; e-mail: information@ica-foundation.org; or go to: <http://www.ica-foundation.org>.

V. Bibliography

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