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Levonorgestrel Intra Uterine System: A Review

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ABSTRACT

An Intrauterine device (IUD) is a small object which is used to prevent pregnancy by inserting it through the cervix into the uterus. There is a small string that hangs down the IUD that leads into the upper part of the vagina. It works by changing the lining of the uterus and fallopian tubes which affects the movements of eggs and sperm thus preventing fertilization. There is currently a wide variety of IUDs available worldwide; some are inert, some are copper-containing, and some are medicated with levonorgestrel or Indomethacin. They also come in a wide variety of sizes and shapes including T-shaped and “frameless” devices. This article focuses specifically on the LNG-IUS, exploring the mechanism of action, insertion procedure, safety, precautions, and variety of uses. LNG-IUS is in the class of medications called progestins that works by preventing the release of an egg from the ovary or by preventing fertilization of the egg by the sperm. It may also work by changing the lining of the uterus to prevent the development of pregnancy.

INTRODUCTION-

Contraceptives are the devices that prevent fertilization. Using various devices can deliberately prevent pregnancy. These are also known as Birth Control Methods. ^[1]IUDs give great, long-term protection against pregnancy. IUDs are one of the most effective methods because of their convenience of use. IUDs are “set-it-and-forget-it” birth control. ^[2]

The contraceptive known as the levonorgestrel intrauterine system (LNG IUS) was developed in the 1970s. The product releases small amounts of progestin into the uterus and improves contraceptive action compared with earlier inert plastic devices. The first commercialized LNG IUS set a high standard for future contraceptive development. Relative to other reversible contraceptives, the LNG IUS has the highest effectiveness levels (combining the highest product continuation rates with over 99% efficacies) ^[3]. The duration of action is 3 to 6 years (likely more), and the product provides important non-contraceptive benefits related to how it thins the lining of the uterus and reduces menstrual blood loss; from these effects, it may alleviate and/or prevent iron deficiency (anemia). However, because of historically high product costs and a variety of other reasons, the LNG IUS is not widely available to women in resource-poor settings ^[4].

The legacy product was first approved in Finland in 1990, in the rest of Europe in the 1990s, and in the United States in 2002; today it is registered in more than 100 countries, and 2014 revenue topped US\$900 million (personal communication with Klaus Brill, Bayer HealthCare Pharmaceutical, June 30, 2015, citing the Bayer Annual Report 2014).^[5] Because of the product’s great success, even at a high retail price, other companies have recently developed similar technologies in the hopes of entering global markets with lower-cost products. Currently, 5 different pharmaceutical companies make an LNG IUS. Two Indian companies had products approved in India in 2011 and 2012, ^[6,7] and a third Indian company might make the product available ^[8]. A Belgian company makes an LNG IUS that was approved in Europe in 2014 and the United States in 2015^[9].

What is Levonorgestrel?

It is a birth control hormonal medication.

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one, the active ingredient in Mirena, has a molecular weight of 312.4, a molecular formula of C₂₁H₂₈O₂, and the following structural formula:

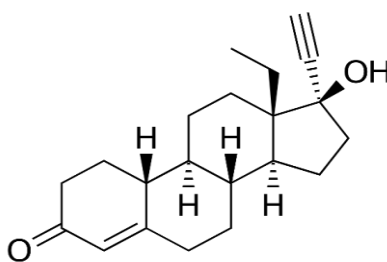


Figure No. 1 Structure of Levonorgestrel

Drug class-Contraceptives, Progestins^[10].

It is the C13 β or laevorotatory stereoisomer and enantiomer a pure form of norgestrel, the C13 α or dextrorotatory isomer being inactive^[11,12]. Levonorgestrel is more specifically a derivative of norethisterone (17 α -ethynyl-19-nortestosterone) and is the parent compound of the gonane (18-methylestrane) subgroup of the 19-nortestosterone family of progestins^[13]. Levonorgestrel acetate and levonorgestrel butanoate are C17 β esters of levonorgestrel^[14, 15]. It has a molecular weight of 312.45 g/mol and a partition coefficient (logP) of 3.8.

About IUDs-

Intrauterine devices (IUDs) are small devices placed in a uterus of a woman to interrupt the process of insemination. IUDs have been on and off the market for decades. They're very popular around the world and are one of the most effective forms of birth control^[16]. The IUDs used these days are considered to be both effective and safe for most women. They are safe to use even if a woman is breastfeeding. A woman is very unlikely to get pregnant while she has an IUD (less than 1% chance).^[17]

Types of IUD:^[18]

1. Copper
2. Hormonal.

Currently, there are four brands of IUDs available: ParaGard is a copper IUD and Mirena, Liletta, and Skyla are hormonal IUDs that use progestin^[19].

IUDs are an excellent choice of birth control for many women. However, they're not the best choice for women who are at high risk for sexually transmitted infections (STIs)^[20].

How does an IUD work?

Both the copper and hormonal types of IUDs work by making it difficult for sperm to reach the egg. ParaGard (copper IUD) causes an inflammation response in the lining of the uterus. This inflammation is toxic to sperm. It also makes the uterus hostile to implantation, if fertilization occurs. ParaGard works for up to 10 years after insertion^[21].

Mirena (IUD) works to thin the lining of the uterus to prevent the transport of sperm into the fallopian tubes where fertilization must occur. The progestin release also thickens the cervical mucus and can prevent ovulation. Mirena can last for up to five years after insertion.^[22]

Skyla and Liletta are smaller and contain a lower dose of progestin. They both thin the uterus lining and can last up to three years^[23].

What is Levonorgestrel Intra Uterine System?^[24, 25]

1. Levonorgestrel is a female hormone that can cause changes in the cervix and uterus. Levonorgestrel intrauterine system is a T-shaped plastic intrauterine device (IUD) that is placed in the uterus where it slowly releases the hormone.
2. Levonorgestrel intrauterine system is used to prevent pregnancy for 3 to 6 years. A female may use this IUD whether she has children or not. Mirena is also used to treat heavy menstrual bleeding in women who choose to use an intrauterine form of birth control.
3. Levonorgestrel is a progestin and does not contain estrogen. Levonorgestrel intrauterine system should not be used as emergency birth control.
4. Levonorgestrel intrauterine system may also be used for purposes not listed in this medication guide.

Mechanism of Action of Levonorgestrel Intra-Uterine System-

The LNG-IUS contraceptive action works by primarily inhibiting fertilization, which is prevented by various local effects within the uterine cavity. Because it functions in this manner, LNG-IUS is not considered efficient^[26].

It works in the following ways

1. With LNG-IUS, the uterine fluid is altered to contain a high amount of white blood cells and different cellular mediators that inhibit sperm motility in the uterine cavity^[27].

2. The cervical mucus is thickened, blocking sperm from passing through the cervix into the uterus and oviduct (Fallopian tube), where fertilization may occur. ^[28]
3. LNG-IUS leads to the thinning and atrophy of the endometrial lining within 3 months of use, as the endometrial estrogen receptors are suppressed by LNG's effect in the uterus. This suppression is the reason why menstrual bleeding is reduced (and sometimes stopped) during LNG-IUS use ^[29].

Insertion Procedure of Levonorgestrel Intra-Uterine System-

Proper LNG-IUS insertion is important for proper positioning within the uterus, lessening the risk of infection, perforation, and expulsion, as well as ensuring uniform dispersion of LNG over the endometrium. ^[30]

The LNG-IUS should be inserted: ^[31]

1. Within 7 days from the onset of menstruation (because of the low likelihood of pregnancy during this time)
2. 6 weeks or longer (until full involution of the uterus) after childbirth.
3. Immediately after menstrual regulation or first trimester spontaneous or induced abortion, provided there is no infection.

Acceptors of LNG-IUS must be screened and cleared of STIs, and it is the providers' responsibility to inspect the woman's reproductive tract, both externally and internally, for signs and symptoms of infection. LNG-IUS acceptors should be counseled before device insertion and provided with an opportunity to ask questions and refuse insertion if desired ^[32].

Structure of Levonorgestrel-releasing intrauterine system: [33]

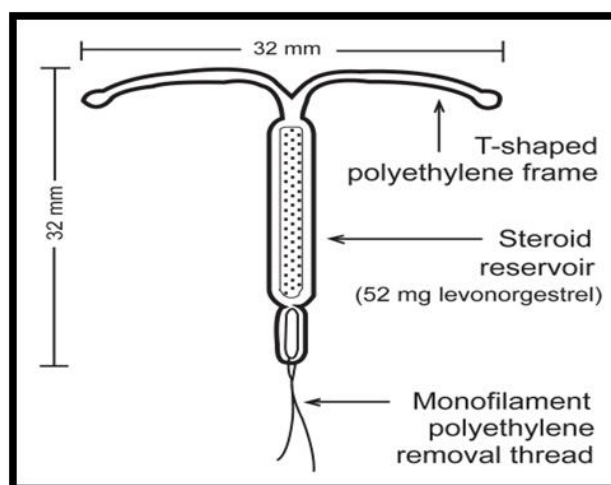


Figure No. 2: Levonorgestrel-releasing intrauterine system (LNG-IUS) [34]

1. The device consists of a T-shaped polyethylene frame (compounded with barium sulfate, making it radio-opaque) along with a steroid reservoir (hormone elastomer core) that surrounds the vertical stem.
2. There is a white or almost white cylinder in the reservoir that is made from the mixture of levonorgestrel and silicone (polydimethylsiloxane) in which the total amount of levonorgestrel is 52mg.
3. The reservoir is covered with a semi-opaque silicone membrane. The length of the T-shaped body is 32mm in both vertical and horizontal directions.
4. A monofilament brown polyethylene thread is attached to the vertical stem of the T-shaped body which is removable; it contains iron oxide as a colorant.

Precautions of Levonorgestrel Intra-Uterine System-

1. Before using this medication device, a woman should inform the doctor if she is allergic to levonorgestrel, or to any other progestin (such as norethindrone, or desogestrel); or she is having any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Before using this product, a woman needs to inform the doctor about her medical history, especially of recent pregnancy, current breastfeeding, bleeding/blood disorders, high blood pressure, abnormal breast exam, cancer (especially endometrial or breast cancer), depression, diabetes, severe headaches/migraines, heart problems (such as heart valve disease, irregular heartbeat, previous heart attack), liver disease

(including tumors), previous pregnancy outside the uterus (ectopic pregnancy), stroke, unexplained vaginal bleeding, uterus problems (such as fibroids, pelvic inflammatory disease-PID), conditions that weaken the immune system/increase the risk of infection (such as HIV, leukemia, IV drug abuse).^[35]

2. Before having surgery, tell the doctor about all the products in use (including prescription drugs, nonprescription drugs, and herbal products). Also, the woman is going to have an MRI test.^[36]

3. This device should not be used during pregnancy. If a woman becomes pregnant or thinks that she may be pregnant, tell the doctor right away. Levonorgestrel passes into breast milk. Consult the doctor before breastfeeding.^[37]

Side effects of Levonorgestrel Intra-Uterine System-^[38-40]

1. Get emergency medical help if signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat, is observed.

2. Get emergency medical help if there is severe pain in the lower stomach or side. This could be a sign of tubal pregnancy.

3. The IUD may become embedded into the wall of the uterus or may perforate (form a hole) in the uterus. If this occurs, the device may no longer prevent pregnancy, or it may move outside the uterus and cause scarring, infection, or damage to other organs. The doctor may need to surgically remove the device.

4. Call the doctor at once under the following conditions:

- a. severe cramps or pelvic pain, pain during sexual intercourse;
- b. extreme dizziness or light-headed feeling;
- c. severe migraine headache;
- d. heavy or ongoing vaginal bleeding, vaginal sores, vaginal discharge that is watery, foul-smelling discharge, or otherwise unusual;
- e. pale skin, weakness, easy bruising or bleeding, fever, chills, or other signs of infection;
- f. jaundice (yellowing of the skin or eyes); or

g. Sudden numbness or weakness (especially on one side of the body), confusion, problems with vision, sensitivity to light.

5. Common side effects may include:

- a. pelvic pain, painful or irregular menstrual periods, changes in bleeding patterns or flow;
- b. vaginal swelling, itching, or infection;
- c. temporary pain, bleeding, or dizziness during insertion of the IUD;
- d. ovarian cysts (pelvic pain that disappears within 3 months);
- e. stomach pain, nausea, vomiting, bloating;
- f. headache, migraine, depression, mood changes;
- g. back pain, breast tenderness or pain;
- h. weight gain, acne, oily skin, changes in hair growth, loss of interest in sex; or
- i. Puffiness in your face, hands, ankles, or feet.

This is not a complete list of side effects and others may occur.

Benefits and Limitations of Levonorgestrel Intra-Uterine System-

Benefits of LNG-IUS use, in addition to highly effective contraceptive action, include: ^[41,42]

1. A long-term reversible method.
2. No daily action is required.
3. Easy insertion and removal (without the need for local anesthesia).
4. The lowest dose of hormonal contraceptive, with no estrogen.
5. Lessening in frequency and amount of menstrual bleeding.

Limitations of use may include:^[43]

1. Spotting and intermenstrual bleeding in the first few months of use.
2. Possibility of hormonal side effects.
3. Insertion and removal are to be done by a trained provider.

Do not use Levonorgestrel Intra-Uterine System in- ^[44-46]

1. Pregnancy
2. Puerperal sepsis
3. Immediately post-septic abortion
4. Unexplained vaginal bleeding that has not been adequately investigated
5. GTN and increasing β -hCG level
6. Cervical cancer awaiting treatment (insertion)
7. Current breast cancer
8. Endometrial cancer (insertion)
9. Ovarian cancer (insertion)
10. Uterine leiomyoma with distortion of the cavity
11. Distortion of the uterine cavity that is incompatible with IUD insertion
12. Current PID or mucopurulent cervical discharge (insertion)
13. Pelvic tuberculosis (insertion)

Marketed information- Levonorgestrel intrauterine device contains 52mg of LNG which is a progestin and is intended to provide an initial release rate of approx. 20mcg/day of LNG. ^[47]

Generic name- Levonorgestrel intrauterine system (LEE voe nor JES trel IN tra UE ter ine SIS tem) ^[10]

Brand name- Kyleena, Liletta, Mirena, Skyla ^[10]

Dosage forms- Intrauterine device (13.5 mg; 19.5 mg; 52 mg) ^[10]

CONCLUSION-

Levonorgestrel is a progestin and does not contain estrogen. The levonorgestrel-releasing intrauterine system (LNG-IUS) is a safe, effective, and acceptable form of contraception used by over 150 million women worldwide. It also has a variety of no contraceptive benefits including treatment for menorrhagia, endometriosis, and endometrial hyperplasia.

Levonorgestrel intrauterine system is used to prevent pregnancy for 3 to 6 years. The LNG-IUS has served as one of the most effective forms of contraception for preventing unintended pregnancy in recent times, with a cumulative global pregnancy rate of <0.5%. The most frequent adverse drug reactions (ADRs) of LNG-IUS are thought to be menstrual irregularities and changes in bleeding patterns. Levonorgestrel intrauterine system will not protect from sexually transmitted diseases, including HIV and AIDS. But still seems to be a good method for birth control.

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