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Review Article

An Overview of the Basic Knowledge of Levonorgestrel-Releasing Intrauterine System

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Abstract

Levonorgestrel-releasing Intrauterine system (LNG-IUS, Mirena) is a very safe, efficient, long-acting and reversible intrauterine device, which releases high-efficiency at a daily dose of 20ug Progesterone mainly acts on the part of the endometrium, causing the endometrial glands to shrink. A large number of studies have fully proved that LNG-IUS is not only effective in contraception, but also widely used in non-contraceptive fields. LNG-IUS is effective in treating gynecological diseases such as menorrhagia and dysmenorrhea. In addition, LNG-IUS is also used in endometriosis, adenomyosis, endometrial polyps, endometrial hyperplasia, and early endometrial cancer. Reversal of cancer and endometrial protection in breast cancer patients. This article will briefly summarize the basic knowledge of LNG-IUS and the clinical application of LNG-IUS in gynecological diseases.

Keywords: Levonorgestrel-releasing Intrauterine system; Mirena; High-efficiency progesterone; Long-acting reversible contraception

Introduction

Levonorgestrel-releasing Intrauterine system (LNG-IUS),its trade name is Mirena. It was originally designed in the 1970s, when the main purpose was to provide safe, efficient, long-acting and reversible contraception (LARC) for women of childbearing age [1]. LNG-IUS is a T-shaped device with a white cylindrical drug core rack on the longitudinal arm, which contains 52mg of levonorgestrel (LNG). The independently designed slow-release system releases 20ug of LNG into the uterine cavity every day. The validity period is 5 years [2]. Currently in China, the approved clinical indications for LNG-IUS mainly include contraception and idiopathic menorrhagia. However, with the continuous deepening of research in recent years, the clinical application of LNG-IUS has become increasingly widespread, and it has already surpassed the scope of approved clinical indications [3]. Based on this, this article will mainly introduce the basic knowledge about LNG-IUS, and briefly summarize the clinical application scope of LNG-IUS and the common confusions and countermeasures of using LNG-IUS.

An Overview of the Basic Knowledge of Levonorgestrel-Releasing Intrauterine System

Levonorgestrel-releasing Intrauterine system (LNG-IUS, Mirena) releases a low blood concentration of levonorgestrel. The blood concentration is reported to be 0.1-0.2ng/ml in the literature [1]. Some key points of knowledge of the Levonorgestrel-releasing Intrauterine system are briefly summarized: ①Levonorgestrel-releasing Intrauterine system contains 52mg of levonorgestrel and releases 20ug of levonorgestrel every 24 hours, the validity period is 5 years [2]. ②What is levonorgestrel (levonorgestrel, LNG)? LNG is a fully synthetic high-efficiency progesterone (sterane synthetic progesterone preparation) It is the optically active form of racemic norgestrel. The progestin activity is twice as strong as norgestrel, which is about 100 Times of norethindrone. Therefore, the dose can be halved compared with norgestrel, and adverse reactions will be reduced accordingly. Levonorgestrel mainly acts on the hypothalamus and pituitary gland, which

significantly reduces or disappears the peaks of FSH and LH levels in the middle of menstruation. The ovaries do not ovulate and have obvious anti-estrogen activity. Its anti-estrogen activity is stronger than norethindrone 10 times(Note: Norethindrone is a synthetic progesterone preparation of estradiol, a synthetic 19-desmethyltestosterone derivative, which has weak estrogenic and anti-estrogenic activity, and has mild androgen Activity and protein assimilation, its androgenic activity is approximately equivalent to 1/6 of testosterone). LNG has almost no estrogenic activity. It can thicken cervical mucus and hinder sperm penetration. It shows strong progesterone activity for the transformation of the endometrium, which can make the endometrium thin, and the endometrial epithelial cells are low columnar, and the secretion function is poor, which is not conducive to the implantation of pregnant eggs. LNG also has a certain androgenic activity and protein assimilation, which can inhibit ovulation by oral or subcutaneous injection [3]. ③The levonorgestrel contained in the levonorgestrel intrauterine sustained-release system is an extremely effective progesterone, which mainly acts locally [4-6]. ④ What is the actual blood concentration of levonorgestrel released by the intrauterine release system of levonorgestrel? It has been reported in the literature that about 10% of levonorgestrel is released in the systemic circulation. Some patients may still have hormone-related complaints, such as breast tenderness, acne, mood changes, weight gain, hair loss, hirsutism or general swelling. Some patients will have functional ovarian cysts. These phenomena are more obvious in the first few months of use and will gradually decrease with the extension of use time. This is actually related to the patients' extreme sensitivity to levonorgestrel [7]. ⑤The concentration of LNG in the blood circulation of women using LNG-IUS is very low and stable. Pharmacokinetic studies have shown that the plasma concentration reached by the LNG sustained-released by LNG-IUS in the uterine cavity is maintained at 0.4-0.6nmol/L (150-200pg/ml) through the intimal basal capillary network to reach the blood circulation. The blood concentration of commonly used oral contraceptives is low, and the concentration in the fallopian tube is also very low [8]. Another study reported that the median blood LNG concentration of women who used LNG-IUS within 7 years was 125-200ng/L [9]. ⑥The Levonorgestrel-releasing Intrauterine system often causes amenorrhea in patients. Isn't menstruation after LNG-IUS a sign of ovarian function decline? Will the patient get older as a result? will not. A large number of studies have confirmed [10-12] that LNG-IUS does not affect the patient's ovarian function, ovarian cycle, and estrogen secretion. The amenorrhea caused by LNG-IUS is mainly caused by the local inhibition of LNG on the endometrium. This inhibition is caused by the local high level of LNG on the endometrial estrogen receptor down-regulation, so that the endometrium is against the endogenous Sexual and exogenous estrogen are not sensitive, and inhibit the intimal hyperplasia reaction, resulting in oligomenorrhea and even amenorrhea after LNG-IUS use. And this inhibition is reversible. After the birth control ring is removed, as long as the patient's ovarian function is present, the normal menstrual cycle can still be restored. After the LNG-IUS is taken out, menstruation can be recovered, and the average recovery time is 23 days. Therefore, the ovaries of patients with LNG-IUS can still secrete E2 hormones normally, and will not cause the increase of FSH, and can have a normal ovulation cycle. ⑦So, what mechanism does the levonorgestrel intrauterine sustained-release system use to exert its high-efficiency contraceptive effect? It mainly includes three aspects: a. Continuous inhibition of the endometrium, which interferes with or is not conducive to the implantation of fertilized eggs; b. Increases the consistency of cervical mucus and inhibits the passage of sperm (the increase in the consistency of cervical mucus can effectively inhibit retrograde infection and reduce the pelvic cavity The occurrence of inflammatory diseases); c. Anti-fertilization: inhibit the activity and function of sperm in the uterus and fallopian tubes, and prevent fertilization [5,9].

Clinical Application of Levonorgestrel-Releasing Intrauterine System

What are the main clinical applications of Levonorgestrel-releasing Intrauterine system? In summary, the main points are as follows [13-24]: ①Long-acting reversible contraception (LARC), which has a contraceptive effect comparable to sterilization; ②Functional uterine bleeding and menorrhagia; ③Resistance to menstruation caused by uterine fibroids More therapeutic effects; ④Therapeutic effect on adenomyosis; ⑤Maintenance treatment after endometriosis; ⑥The effect of LNG-IUS in relieving dysmenorrhea; ⑦The protective effect of endometrium in HRT; ⑧Tamoxifen treatment after breast cancer surgery Endometrial protection; ⑨impact on endometrial hyperplasia and endometrial cancer.

The 2016 British Endometrial Hyperplasia Management Guidelines pointed out that for the hormone treatment of endometrial hyperplasia, the Levonorgestrel-releasing Intrauterine system is listed as the first choice. Progesterone therapy is prioritized to recommend the Levonorgestrel-releasing Intrauterine system, that is, Mirena (LNG-IUS× at least 6 months, preferably × 5 years for those without a childbirth plan), which can obtain a higher remission rate. According to the 2016 UK Endometrial Hyperplasia Management Guidelines and the 2017 China Endometrial Hyperplasia Diagnosis and Treatment Consensus [25-26], for the treatment of endometrial hyperplasia, whether it is the treatment of no dysplasia or atypical hyperplasia, LNG-IUS seems to have been Placed in a very important position, this is slightly different from the previous view (the dysplasia should be converted with high-efficiency progesterone before considering the placement of LNG-IUS maintenance therapy [27-29]). However, whether these new ideas can be widely and consistently adopted remains to be confirmed by the test of time and further research.

Common Confusion and Countermeasures in the Clinical Use of Levonorgestrel-Releasing Intrauterine System

What are the main problems and confusions in the clinical use of Levonorgestrel-releasing Intrauterine system? In summary, the main points are as follows: ①Irregular vaginal bleeding often occurs during the first half of the year after using LNG-IUS. If the amount of vaginal bleeding is small, it can be observed without special treatment; if the patient is worried and urgently requires treatment, you can try estrogen therapy according to the following plan: low-dose compound oral contraceptives- compound LNG tablets (ethinyl estradiol 30μg / LNG150μg), one tablet a day for 22 days; ethinyl estradiol 50μg once a day for 20 days; estradiol valerate 2mg, continuous use for two months [22]; ② Patients with adenomyosis have a large uterine cavity and should not be placed directly. Consider three injections of GnRH-a and wait for the uterus to shrink before placing it (uterus <8 weeks of gestation, can be placed directly ; uterus> 8 weeks of gestation, placed after GnRH-a is used, it is recommended to place a birth control ring when menstruation is not regained) [23]. ③The problem of the birth control ring moving down or falling off [30]. Lowering the birth control ring often causes increased vaginal bleeding. Therefore, for patients with significantly increased vaginal bleeding after LNG-IUS placement, it is necessary to consider the possibility of the contraceptive ring moving down or completely falling off. For such patients, if the contraceptive ring does not protrude out of the uterine cavity, consider pushing the contraceptive ring up after disinfection to maintain the handle of the contraceptive ring above the internal cervix. It does not necessarily require the position of the contraceptive ring to be in the middle of the uterine cavity (the uterine cavity is often very Difficult to do). If the birth control ring completely protrudes out of the uterine cavity, it is not recommended to re-enter the original ring into the uterine cavity [13,22]. ④For patients with large uterine cavity, can a T-ring be placed at the same time as LNG-IUS to prevent the contraceptive ring from moving down or falling off? First of all, the efficacy of this approach is not clear; secondly, it does not meet the criteria for diagnosis and treatment. Therefore, it should be used with caution.

Summary and Outlook

In summary, the Levonorgestrel-releasing Intrauterine system not only has a long-term and reversible effect in contraception, but also has a wide range of non-contraceptive clinical applications and good results. However, there are also many problems in the clinical application of Levonorgestrel-releasing Intrauterine system, which confuses clinicians. In order to facilitate memory, the author compiled the essentials of the Levonorgestrel-releasing Intrauterine system (Mirena) for your reference:

- Mirena ring is very different and contains levonorgestrel;
- In fact, high-efficiency progesterone, the local effect is very sufficient;
- The concentration of hormones in the blood is low, and the blood drug level is stable;
- Complications take place in the initial use;
- Often cause amenorrhea, and ovarian function does not decline;
- The inhibitory effect is often reversible, and ovarian hormones are still secreted;
- The contraceptive effect can be assured;
- Mirena has many effects, such as stopping bleeding, relieving pain and protecting the endometrium;

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Conflict of Interest

Authors declare no conflict of interest.

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