Review Article

The slow levonorgestrel-releasing intrauterine system (LNG-IUS) 20 mcg/day: a literature review

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Summary

The aim of the study is to present the mechanisms of action, indications, complications, contraindications and the necessary tests before the insertion of a levonorgestrel-releasing intrauterine system (Mirena). After a literature search in Pubmed, a narrative review in the field is presented.

Key words: Intrauterine devices; Levonorgestrel; Fertility; Metrorrhagia; Fertility; Ectopic pregnancy.

Introduction

The slow levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena) is a simple Nova T IUD, made of polyethylene, while its vertical stem is saturated with 52 mg levonorgestrel mixed with PDMS (polydimethyl siloxane). The 19-nor progestin (LNG) is released at a pace of 20 mcg/24 h during the first year of use, whereas the latter is reduced to 11 mcg/24 h within the next five years [1-3]. Thus, the mean value of its release is about 14 mcg/24 h for the approved [4] 5-year period of usage [5].

The first slow release intrauterine device contained progesterone; it had a one-year duration of action and was marketed some 30 years ago. However, it was withdrawn from the market because of a relevant increase in the percentage of extrauterine pregnancies, since increase of the ratio between the percentage of ectopic pregnancies and the corresponding one of intrauterine pregnancies, was established in comparison with their ratio in the general population. In the meantime, a device releasing synthetic progestin levonorgestrel was being developed and it has been successfully marketed [6].

Literature review

We searched for relevant publications in the Pubmed database up to March 2009. The key words used included the terms: "Mirena", "levonorgestrel", "intrauterine device", and "levonorgestrel-releasing intrauterine system pelvic floor reconstruction". In addition, we reviewed the references of the initially retrieved articles to identify additional relevant publications. We focused on articles describing the mechanisms of action, indications, complications, contraindications and necessary tests before the insertion of the slow LNG-IUS (Mirena). We identified 3,787 articles with the computerized search. The information found in 37 articles of this search was used to form our narrative review.

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LNG-IUS overview

Mechanisms of action and intrauterine environment

The endometrium becomes atrophic under the influence of an IUD with further repercussion on the implantation of the fertilized ovum, which becomes difficult. Thus about 20% of the women with the LNG-IUS have extremely scanty or no period at all during the first year after its insertion [2]. Histologically, by using several methods (like transmission electron microscopy, light microscopy and scanning electron microscopy), we observed that the glandular columnar epithelium becomes gradually thinner and more cuboidal, during mainly the first six months of use of the device; additionally, after the sixth month, it keeps on becoming thinner and the cells appear to be even more cuboidal. The microvilli of the epithelial cells are more numerous, but appear shorter. The basal lamina is wavy, but remains uniform and regular, while the matrix below appears looser. Epithelial cell projections, through the basal lamina, seem to bring endometrial epithelium-stroma into communication with each other. Consequently, the differentiation and function of the endometrial epithelium that may be guided and controlled through these links (during the normal menstrual cycle) become fewer in number and less complex in shape. The epithelial stroma appears quite edematous during the first month, but later, after the first trimester of use, it subsides gradually and becomes more compact (the numbers of collagen fibrils increase) showing neutrophil infiltration, while in the meantime, the cells are being decidualized. It was also noted that the junctional complexes between the epithelial cells, which are normally loosened during the implantation of blastocysts, persist as far as their number and stage of development is concerned, under the action of levonorgestrel, thus preventing the blastocyst to breach the surface of the uterine epithelium. Additionally, neither pinopodes nor the nucleolar channel system (NCS) are observed, something that may contribute to the contraceptive effect of the LNG-IUS according to the study of Pakarinen *et al*.

[2]. This change of the endometrium is possible to demonstrate with the help of ultrasonographic scans in patients who use the LNG-IUS > 3 months (group A). At the same time, a comparative study can take place between them and women using copper IUDs for an almost equal, on average, period of time (group B), as the study of Zalel *et al*. characteristically describes. Endometrial width appears to be thin (4.1 mm on average) and it differs from the corresponding one of women who carry the copper IUD (mean value 7.3 mm), while no difference is reported in the resistance index (RI) of the cervical branch of the uterine arteries between these two groups. On the contrary, blood flow in the spiral arteries of group A was extremely reduced in 75% (while this phenomenon was not noticed in group B). Together with the thickening of the arterial walls, the capillary thrombosis and reduction in the endometrial width, this explains the fact that amenorrhoea or only slight menstrual bleeding was achieved in 87% of patients in group A, whereas 34% of the patients in group B reported menorrhagia or intermenstrual bleeding [3]. The above showed a different (than expected in the normal menstrual cycle) configuration of the endometrial environment. It seems to reflect the preclusion of the transition into a receptive for the implantation of the fertilized ovum, gene expression in the cells, which may take place on the grounds of several influences of the IUD on the genes that are involved in the preparation, and receptivity of the endometrium. The study of Horcajadas *et al*. [7] showed that with the presence of an IUD in the endometrial cavity, 147 genes with known identity are dysregulated (78 genes up-regulated, 69 genes down-regulated), 52 of which refer to genes that are related to the creation of the window of implantation. It was obvious that two months after the removal of the IUD, the endometrium continued to present a dysregulated gene expression (in 96% of the genes that were studied), whereas, one year later the latter becomes normal in a large portion (80%), just like it is before the insertion of the device. Of course, this study refers to IUDs at large, while extended research is required to be done for each type of IUD. Additionally, the reduction of the possibility for a woman to get pregnant just after the removal of the IUD can be explained through the above mechanism.

Fertilization

By promoting the production of glycodelin A (GdA/PP14), which is a progesterone-dependent glycoprotein with contraceptive action from the endometrial cells, the LNG-IUS inhibits binding of sperm to the zona pellucida. Normally this substance is absent from the endometrium during the proliferative and immediate postovulatory phases of the cycle, permitting the coupling of male and female gametes, but it is produced during the middle (5^{th}-6^{th} day after the ovulation) and late secretory phase of the cycle. According to the study of Madelin *et al*. [8], with the help of immunohistochemistry, in situ hybridization and statistical analysis, it was established that the endometrium from all women who were carrying the LNG-IUS contained GdA mRNA and protein during the midcycle, despite the duration of IUD usage. In comparison, the concentration of these substances was studied in women wearing Cu-IUDs and it was established that the concentration was less frequent among them than in a population with the LNG-IUS. This "inappropriate" GdA production during the menstrual cycle seems to enhance the contraceptive action of the device.

Other mechanisms of action

It has been shown that the cervical mucus becomes reduced [9] and thicker in women with the LNG-IUS [10] and the characteristic fern-like crystallization is absent, making the environment hostile to the passage of spermatozoa through the female genital tract [4].

However, some studies report that the quality of the mucus is good in 69% of women who have the LNG-IUS and have ovulatory cycles. Research has shown that the endometrial device interferes with the development of the ovum and the ovulation, possibly through subtle disturbances in the hypothalamic-pituitary system and, consequently, in the secretion of gonadotrophins [11]. Nevertheless, ovulation is successful in a portion > 75% of women using the LNG-IUS [9].

Indications

The LNG-IUS has many advantages in confronting several diseases, covering a wide spectrum of ages, from the very first years of menstruation [the LNG-IUS is better than other IUDs in adolescence because of its better menstrual profile – easier cycles as well as elimination of dysmenorrhoea] [10] until later, after menopause [12].

Contraception

It has been established by the research of the last two decades that the risk of IUD failure (which is directly translated into the possibility of an upcoming and undesirable pregnancy) is < 2% in five years for women who use such devices and, more specifically, concerning the LNG-IUS, the risk is < 0.5% (in five years) [13]. In another study, it was reported that the percentage of failure is < 0.2/100 women/years and that in a 7-year period, pregnancies reach 1.1% [14]. The success of the LNG-IUS compared with other IUDs is described in the study of Thonneau *et al*. [15], in which women using Mirena (as the control population) are defined as having a pregnancy risk = 1, with GyneT380, MLCu375 and Gynelle 375 to have a risk = 2.70, with Sertalia = 8.45, with Nova T = 7.20 and with GyneFix = 24.43. The possibility of IUD failure seems to be related positively with the history of previous expulsion of the device (one out of 20 patients) [10], which reflects the possible adverse conditions for retaining it in the endometrial cavity (small uterus, e.g., in adolescents), anomalies in its morphology and its position/tilting, which results in the device being in an inappropriate position after its insertion and, conse-

quently presenting a default action and effectiveness. Anti-inflammatory drugs, history of polyps, leiomyomas, abortion or previous pregnancy with IUDs have not been determined to affect the effectiveness. As a contraceptive the use of Mirena (according to its license) [4] has been defined to be five years, but it has been shown to provide protection for another two years [10, 16]. As far as emergency contraception is concerned, the LNG-IUS is not shown to be effective [9, 17].

Menorrhagia

Excessive blood loss (> 80 ml) during menstruation applies to > 10% of the cases that are referred to gynecologists [18]. The intrauterine system LNG achieves high concentration in the endometrial cavity (470-1500 ng/g of tissue), much higher than achieved with systematic administration of LNG, thus explaining the significant portion of amenorrhea that is observed [12]. In sudies, it has been established that the LNG IUS reduces 94% of the blood loss in idiopathic menorrhagia in the first trimester and it is a more satisfying method for the patient in comparison with the per-os treatment (norethisterone 5 mg x 3) [19]. On the other hand, the effectiveness of this less aggressive method is lower than the corresponding one of hysterectomy (about 100%) for the treatment of dysfunctional uterine bleeding. However Clarke *et al*., found that more than one-third of women, who undergo hysterectomy for episodes of menorrhagia have a normal uterus. This idea together with the fact that the LNG-IUS is a more appealing method for patients with dysfunctional uterine bleeding than hysterectomy (~95% of the women who were asked prefer the device if the success rate of this method in use is > 50%) makes this therapeutical approach to menorrhagia quite attractive [18]. Moreover, it has been concluded that it is a quite effective therapeutic method in women with heavy menses and hemostatic disorders [20].

Hyperplasia of the endometrium

It has been estimated that there are approximately 200,000 new cases of endometrial hyperplasia per year in the Western world. Usually, women go to a physician because of irregular uterine bleeding, and hyperplasia is diagnosed after investigation: non atypical (simple, complex) or atypical (simple, complex) hyperplasia. The study of Haimovich *et al*. reported that in patients (peri- or post-menopausal) with simple non atypical hyperplasia of the endometrium and two years of follow-up under the action of the LNG-IUS a 50% reduction of bleeding was noticed at three months and no bleeding at all in 24 months, while at 12 months, atrophic endometrium was seen in 93.3% of the cases (secretory endometrium in 6.7%) and in 24 months the endometrium became atrophic in 100% of the subjects [21]. In perimenopausal women, in whom the function of the ovaries is not stable as expressed by the estradiol levels (E2) in the serum, there is an increased risk of hyperplasia due to insufficient secretion of progesterone. The same happens in women with HRT. The device stops abnormal uterine bleeding (~83-88% after the first 4 months post-insertion) and protects women effectively from endometrial cancer for four years after its insertion [3] by inhibiting, with the action of progestagen, the estrogen-dependent development of the endometrium. It is worth mentioning that women with the LNG-IUS who undergo HRT treatment have the same, as the general population, possibility of developing breast cancer and less morbidity from cardiovascular diseases, especially if HRT commenced from the onset of menopause. At large, if HRT and progestagens that achieve high concentrations in the plasma begin years (and not at the onset) after menopause (> 10 y), then it can be harmful for the cardiovascular system, as the preexisting plaque in the vessel walls may be more likely to rupture. In contrast, with progestagens that achieve low concentrations in the serum like the released levonorgestrel of the LNG-IUS, the above risk is very low [12].

Recently, a study was published [22] in which 105 patients > 40 years old with episodes of abnormal uterine bleeding (menorrhagia/menometrorrhagia that could not be managed with conservative therapy in 37/105 individuals and postmenopausal bleeding and spotting under HRT or tamoxifen in 68/105 individuals) underwent treatment with the LNG-IUS with observation (with histological examination of the endometrium – endometrial Pipelle sampling) at three months and six months post-insertion, and 6-monthly intervals thereafter in all cases. Of the patients, 16/105 had simple non atypical hyperplasia of the endometrium, 80/105 complex non atypical, and 9/105 atypical hyperplasia. The results were: 94/105 had regression of the disease (= several degrees glandular atrophia and metaplasia of the endometrium) in 24 months post LNG-IUS insertion (90/105 in the first year; mean time-period of regression (95%) was the first 9 months), with 7/94 reversion of hyperplasia at the 2-year-follow-up. The failure of this method was 18/105. To be more specific, simple non atypical hyperplasia cases regressed (in 24 months) in 15/16, complex non atypical hyperplasia in 73/80 and atypical hyperplasia in 6/9, as can be seen in Table 1.

We noted that the LNG-IUS is quite effective in treating endometrial hyperplasia, despite the histological category [2-year regression rate: 92% (88/96) in non-atypical (simple and complex) hyperplasia, 67% (6/9) in atypical hyperplasia]. It seems that the device will contribute in an effective way in the reduction of hysterectomies in several cases of endometrial hyperplasia, thus dramatically diminishing physical as well as psychological consequences of the operation.

Adenomyosis

A gynecological disorder of undefined etiology and is characterized by the presence of heterotopic endometrium (glands, stroma) into the myometrium, with adjacent smooth muscle hyperplasia. Metrorrhagia and dysmenor-

Table 1.

	Regression of hyperplasia at 24 months			
	Regressed hyperplasia (after 2 years follow-up)	Regressed hyperplasia in 24 but reversion of hyperplasia (after 2 years follow-up) all non-atypical in Pipelle sampling	Persisting hyperplasia	
Simple non-atypical hyperplasia	14 1 case turned out to have acquired atypical hyperplasia, after hysterectomy performed (because of patient's reque)	1	1	16
Complex non-atypical hyperplasia	69 (one case had Stage 1B ovarian cancer)	4	7 (one case had endometrial cancer Stage 1A)	80
Atypical hyperplasia	4	2	3	9
Total	87	7	11	105

rhea are the prevalent and more common symptoms and are found in about 65% of women with adenomyosis. Diagnosis is based on histological examination and, in many cases, is only made at the time of hysterectomy. The study of Bragheto *et al*., counting on magnetic resonance imaging (MRI) for an accurate, noninvasive method of diagnosis, with high sensitivity and specificity ranging from 86% to 100% in symptomatic women, describes the advantages of using the LNG-IUS as a therapeutic method in these patients. It has been established that the maximal junctional zone thickness (JZ_{max}), best demonstrated on T_2-weighted images as the hypotense area between the myometrium and the endometrium (women with adenomyosis: $JZ_{max} > 12$ mm or 8.0-11.9 in some other cases) is reduced to 24.2% in 89.6% of the patients with the LNG-IUS, who are reexamined at three and six months post insertion. At the same time, a significant improvement of menorrhagia and dysmenorrhoea is observed [23].

Endometriosis

A gynecological condition that appears in 7-10% of women in the general population and up to 50% of premenopausal women [10]. In several studies on patients with this syndrome many scientific outcomes have been noted, comparing the use of the LNG-IUS with more conservative treatments in alleviatiating the chronic pelvic pain (CPP) that is related to endometriosis and improving its staging, like the randomized clinical trial of Carlos *et al*. [1]. The aim of this trial was to compare the effectiveness in six months between the use of the LNG-IUS and administration of GnRH analogues in the treatment of patients with endometriosis. The results showed that although women with the LNG-IUS present more episodes of vaginal bleeding (which improved after the 3rd month) and breast tension, the effectiveness of the method when confronting CPP and improving the staging of the disease is equal to the administration of GnRH analogues; while hypoestrogenism, which the latter cause and consequently becomes a reason to stop the treatment, mainly because osteoporosis (they are used only for 6 months; otherwise, hormone therapy should be added), can be avoided (normal serrum levels of estradiol -E2- in patients with the LNG-IUS) [24]. The absence of this major side-effect of the device is supported by the study of Bahamondes *et al*. [24], in which no difference was observed concerning bone mineral density (BMD) of the nondominant forearm between a group of women using Mirena for seven years and a group with TCu380A. Additionally, the BMD measurements were similar to the expected values for women in the same age group as the participants (Z-score) (WHO, 1994). It is concluded that the LNG-IUS can be used safely and for an adequate period of time in the treatment of endometriosis, and thus is a cost-effective solution for the patients [1].

Leiomyomas of the uterus

Research is going on to determine a probable beneficial role of the LNG-IUS in patients with leiomyomas. It seems that the device treats episodes of metrorrhagia in patients, but it does not seem to significantly change their size [25, 26]. However, Mirena is not used when there are fibroids that distort the uterine cavity, as is clearly described in the contraindications of the product [4].

Complications

Abnormal vaginal bleeding: unscheduled breakthrough bleeding (BTB). This is a side-effect of the device which mainly occurs in the first three to six months after insertion. It presents as a spotting vaginal bleeding, which may compel the patient to stop using the IUS, and it was found in about 14% of the women who use it [27]. The possible positive relationship with BTB, (during the first 3 months) of adrenomedullin (AM), a substance that is expressed regularly in the endometrium and, together with vascular endothelial growth factor (VEGF) [28], has angiogenic properties and both seem to be important during the normal menstrual cycle.

In women using the LNG-IUS, AM and VEGF are dys-

Fig. 1

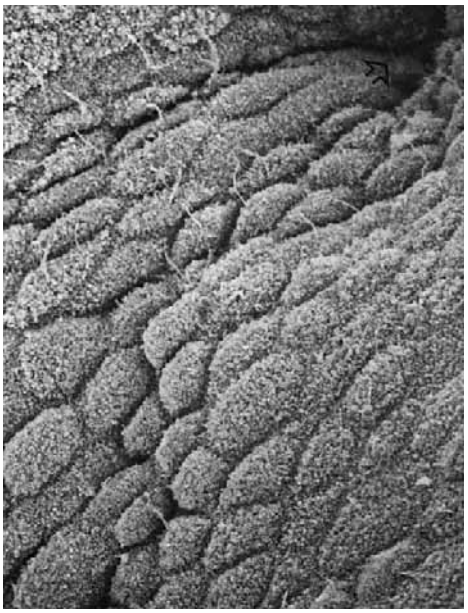

Fig. 2

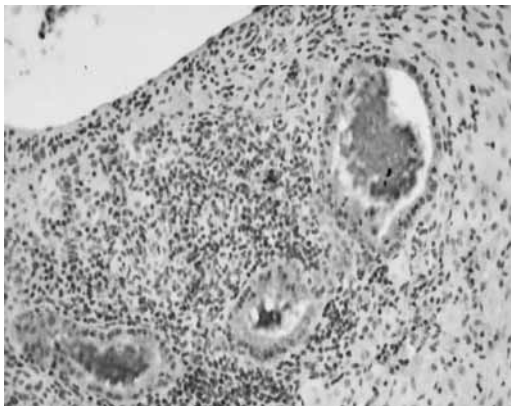

Fig. 3

Figure 1. — Levonorgestrel-releasing intrauterine system.
Figure 2. — The endometrial surface has a smooth and flattened morphology - note a glandular opening at the upper right corner.
Figure 3. — Histological features after LNG-IUS use.

regulated (AM: up-regulation, VEGF: down-regulation): this is an alteration that points the way toward researching BTB etiology for these two substances for the first three months after insertion of the device in the uterus. The values of AM in women three years after the insertion of the IUS (Hague *et al*. 2002) [29], were different (reduced) in comparison with the corresponding ones of the first three months. A factor which justifies this deviation seems to be (apart from the different method that was followed) the duration of its use which is significant [30]. Consequently, we should ask for more mechanisms to explain unexpected hemorragia which happens after long-term use of the LNG-IUS; mechanisms that have remained unclear so far.

Although abnormal bleeding is rare after prolonged (> 6 months) use of the LNG-IUS [there is a negative connection of the primitive spotting vaginal bleeding with the duration of IUD use, so that the portion of amenorrhoea is increased (about 20%) with long-term use], it is reported that it does happen and may become a reason to discontinue its use. Endometrium exposed to progestagen appears to have some large thin-walled venule-like blood vessels, apart from a decreased number of spiral arterioles and reduced density of normal capillaries. These vessels are considered as the possible cause of hemorragia, but their role and cause of their existence must be investigated further. It seems that the reason for the prolonged or relapsed bleeding must be investigated in the disturbance of vascularization or in the alteration of blood vessel function, which is a result of the periodic changes of ovarian steroidal hormones, the local effect of levonorgestrel (reduction in the number of progesterone receptors and, consequently, insufficient support of the endometrium), and some other tissue factors (VEGF-A,B,C and D, receptors VEGFs 1,2,3 and other molecules). The study of Möller *et al*. focused on several differences in VEGFs and their receptors (R) between women with the LNG-IUS (> 6 months) and abnormal bleeding and women with the LNG-IUS without bleeding [26]. When the endometrium becomes very atrophic by the action of the device, vessel abnormalities cause BTB to subside, showing a possible relation between endometrial atrophy and elimination of the side-effect [12].

In practice, if hemorragia persists, then it is useful to check the endometrial cavity (for example US, biopsy) to exclude other conditions [31].

Perforation of the uterus and migration of the IUS is a complication that concerns about 0.9% of insertions of the device in the endometrial cavity. The possibility of uterine perforation from the IUS during this procedure relates positively to the difficulty that gynecologists prefer insertion of Mirena in the uterus and it depends on the experience of the gynecologist, the possible anatomical abnormalities of the cervix, and the cervical canal or the anomalies of the uterus position and morphology, and the history of previous birthgiving [5] as well as on the age of the patient.

It is reported that in adolescents, unlike in adults, the insertion of the IUS is more difficult and painful (86%) [10] something that is also likely to happen in postmenopausal women with an atrophic uterus [12]. However, perforation can happen at any time after the insertion, resulting in migration of the device into the pelvic or peritoneal cavity. Surgical removal of the object from the abdominal cavity is performed to reduce the morbidity and mortility of this complication, which becomes difficult if other diseases co-exist [32]. Migration of an IUD has even been described into the bladder (intravesical) [33].

Fig. 4

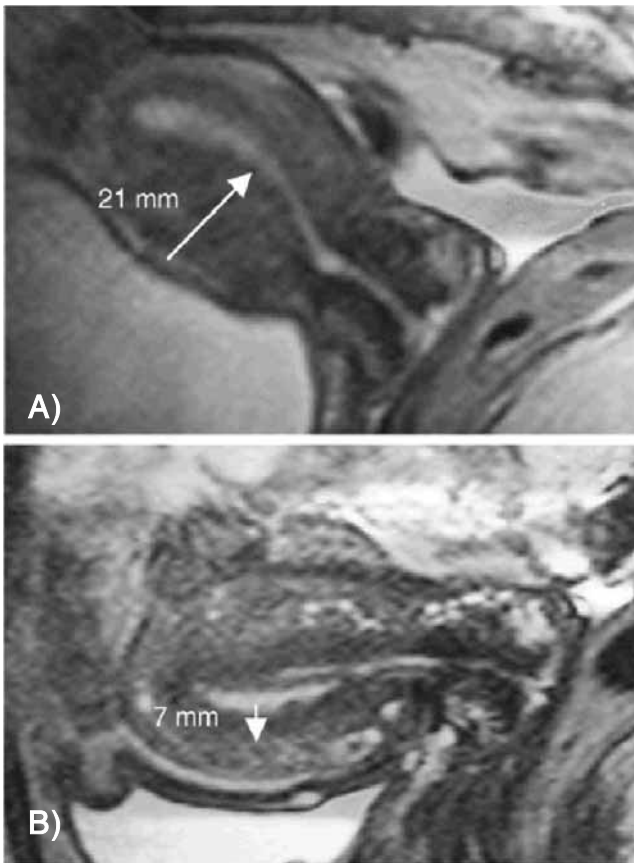

Figure 4. — Comparison of the junctional zone thickness by MRI before insertion (A) at 21 mm and after 6 months of use (B) of the LNG-IUS at 7 mm.

Fig. 5

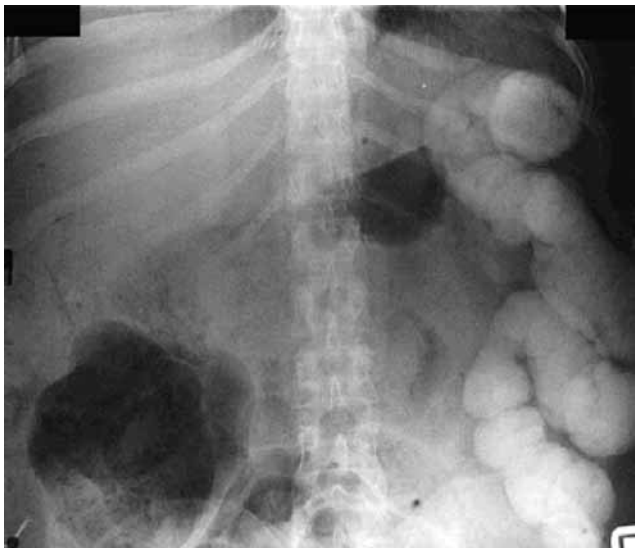

Figure 5. — Abdominal X-ray: LNG-IUS abutting the abdominal wall.

Pelvic inflammatory disease (PID)

The LNG-IUS is, at large, a safe intrauterine device as regards the risk of inducing PID. In the literature, it is reported that the IUS has a reduced risk for PID in comparison to copper devices due to the production of thick cervical mucus and to atrophy of the endometrium. Additionally, the absolute risk for PID is very low and slightly enhanced during the first 20 days after IUD insertion (9.7%). From the 21st day until the eighth year of use, the risk remains almost constant and the same as for the general population (1.4%). Research has shown that the frequency of PID is 0-2.0% when there is not any present infection in the cervix or the uterus and 0-5% in the other cases [10]. In countries, such as Africa, where the prevalence of sexually transmitted disease (STI), like gonorrhea and chlamydial infections, is very high the frequency of PID is expected to be increased. Apart from STIs, different bacteria can creep into the uterus from the vagina or outer environment during the insertion of the device, particularly if there is not sufficient antisepsis [34].

Pelvic actinomycosis is a serious disease, which is attributed to specific microorganisms, the actinomyces-like organisms (ALOs). The latter are frequently found in Papanicolaou tests in asymptomatic women with IUDs. It was established by examining Papanicolaou-stained smears [35] that the prevalence of ALOs(+) was lower in women with the LNG-IUS than in women with copper IUDs (ML375).

Ectopic pregnancy

IUDs reduce the incidence of intrauterine pregnancy as well as the corresponding one of extrauterine pregnancy. Consequently, women who use IUDs have less risk (0.02/100 women/years) for ectopic pregnancy than women who do not use the device (0.3-0.5/100 women/years) [36]. However, there are studies which support the relevant increase of ectopic pregancy in LNG-IUS users, which means that, although this pregnancy is rare, when it happens the possibility of being extrauterine is quite high [37].

Subfertility

The study of Horchadas *et al*. [7] reports that return to fertility after IUD removal is reduced for the first three months (depending on the type of IUD), whereas one year later it approaches 90%. This is attributed to the disturbance of cell gene expression by the IUD, which persists (96%) two months after its removal, while it becomes 80% normal (almost like before the use of the device) in the first year.

Other side-effects

Since levonorgestrel exhibits some androgenic properties, some mild side-effects can be observed, mainly in the beginning of IUS usage. The most common ones are change of mood, acne, headache, breast tension, hirsutism and change in body weight [12].

Contraindications

According to the product labeling [4], the LNG-IUS (Mirena) is contraindicated to be used in the following: known or suspected pregnancy; undiagnosed abnormal genital bleeding; congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity; current genital infection; current or recurrent pelvic inflammatory disease; postpartum endometritis, infected abortion during the previous three months; cervicitis; cervical dysplasia; uterine or cervical malignancy; past attack of bacterial endocarditis or of severe pelvic infection in a woman with an anatomical lesion of the heart or after any prosthetic valve replacement, active or previous severe arterial disease, such as stroke or myocardial infarction; liver tumor or other acute or severe liver disease; conditions associated with increased susceptibility to infections; acute malignancies affecting the blood, or leukemia except when in remission; recent trophoblastic disease while hCG levels remain elevated; and, hypersensitivity to the constituents of the preparation.

Necessary tests before the insertion of the system

IUDs may be inserted anytime during the menstrual cycle. Documentation of a negative pregnancy test is prudent. Insertion may be performed during menstruation to provide additional reassurance that the woman is not pregnant. If insertion is planned during the luteal phase, another nonhormonal contraceptive should be used until after the next menses. A pregnancy test can be done, but the patient should be made aware that a pregnancy test at this time cannot always rule out early pregnancy.

An IUD should not be inserted in a woman with an STD. The American College of Obstetricians and Gynecologists recommends a pelvic examination before insertion to screen for chlamydia and gonorrhea [38].

A Pap test it is also recommended before insertion in order to exclude cervical dysplasia or malignancies [39].

Conclusion

The levonorgestrel-releasing intrauterine system is a relatively new option in the treatment of different gynecologic entities. The indications, complications and contraindications of such a therapeutic system have been reviewed.

References

[1] Petta C.A., Ferriani R.A., Abrao M.S., Hassan D., Rosa E., Silva J.C. *et al*.: "Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis". *Hum. Reprod.,* 2005, *20*, 1993.

[2] Pakarinen P.I., Lähteenmäki P., Lehtonen E., Reima I.: "The ultrastructure of human endometrium is altered by administration of intrauterine levonorgestrel". *Hum. Reprod.,* 1998, *13,* 1846.

[3] Zalel Y., Shulman A., Lidor A., Achiron R., Mashiach S., Gamzu R.: "The local progestational effect of the levonorgestrel-releasing intrauterine system: a sonographic and Doppler flow study". *Hum. Reprod.,* 2002, *17,* 2878.

[4] Schering Health Care Ltd. Mirena: Summary Product Characteristics (SPCs).2002. http://www.medicines.org.uk

[5] Zhou L., Harrison-Woolrych M., Coulter D.M.: "Use of the New Zealand Intensive Medicines Monitoring Programme to study the levonorgestrel-releasing intrauterine device (Mirena)". *Pharmacoepidemiol Drug Saf.,* 2003, *12,* 371.

[6] Benagiano G., Gabelnick H., Farris M.: "Contraceptive devices: intravaginal and intrauterine delivery systems". *Expert Rev. Med. Devices.,* 2008, *5*, 639.

[7] Horcajadas J.A., Sharkey A.M., Catalano R.D., Sherwin J.R., Domínguez F., Burgos L.A. *et al*.: "Effect of intrauterine device on the gene expression profile of the endometrium". *J. Clin. Endocrinol. Metab*., 2006, *91,* 3199.

[8] Mandelin E., Koistinen H., Koistinen R., Affandi B., Seppälä M.: "Levonorgestrel-releasing intrauterine device-wearing women express contraceptive glycodelin A in endometrium during midcycle: another contraceptive mechanism?". *Hum. Reprod.,* 1997, *12,* 2671.

[9] FFPRHC Guidance: "The levonorgestrel-releasing intrauterine system (LNG-IUS) in contraception and reproductive health". *J. Fam. Plan. Reprod. Health Care*, 2004, *30*, 99.

[10] Gold M.A., Johnson L.M.: "Intrauterine devices and adolescents". *Curr. Opin. Obstet. Gynecol*., 2008, *20,* 464.

[11] Barbosa I., Olsson S.E., Odlind V., Goncalves T., Coutinho E.: "Ovarian function after seven years' use of a levonorgestrel IUD". *Adv. Contracept*., 1995, *11,* 85.

[12] Sitruk-Ware R.: "The levonorgestrel intrauterine system for use in peri- and postmenopausal women". *Contraception,* 2007, *75* (suppl. 6), S155.

[13] Thonneau P.F., Almont T.: "Contraceptive efficacy of intrauterine devices". *Am. J. Obstet. Gynecol.,* 2008, *198*, 248.

[14] Sivin I., Stern J.: "Health during prolonged use of levonorgestrel 20 micrograms/d and the copper TCu 380Ag intrauterine contraceptive devices: a multicenter study. International Committee for Contraception Research (ICCR)". *Fertil. Steril*., 1994, *61,* 70.

[15] Thonneau P., Almont T., de La Rochebrochard E., Maria B.: "Risk factors for IUD failure: results of a large multicentre case-control study". *Hum. Reprod.,* 2006, *21*, 2612.

[16] Sivin I., Stern J., Coutinho E., Mattos C.E.R., el Mahgoub S., Diaz S. *et al*.: "Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the copper T380 Ag IUDs". *Contraception,* 1991, *44,* 473.

[17] a) FFPRHC Guidance: "Emergency contraception". *J. Fam. Plan. Reprod. Health Care,* 2006*, 32*, 121.
b) Bhathena R.K.: "Emergency contraception and the LNG-IUS". *J. Fam. Plan. Reprod. Health Care,* 2006, *32*, 205.

[18] Bourdrez P., Bongers M.Y., Mol B.W.: "Treatment of dysfunctional uterine bleeding: patient preferences for endometrial ablation, a levonorgestrel-releasing intrauterine device, or hysterectomy". *Fertil. Steril*., 2004*, 82*, 160.

[19] Irvine G.A., Campbell-Brown M.B., Lumsden M.A., Heikkilä A., Walker J.J., Cameron I.T.: "Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia". *Br. J. Obstet. Gynaecol.,* 1998, *105,* 592.

[20] Lukes A.S., Reardon B., Arepally G.: "Use of the levonorgestrel-releasing intrauterine system in women with hemostatic disorders". *Fertil. Steril.,* 2008, *90,* 673.

[21] Haimovich S., Checa M.A., Mancebo G., Fusté P., Carreras R.: "Treatment of endometrial hyperplasia without atypia in peri- and postmenopausal women with a levonorgestrel intrauterine device". *Menopause,* 2008, *15,* 1002.

[22] Varma R., Soneja H., Bhatia K., Ganesan R., Rollason T., Clark T.J., Gupta J.K.: "The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia - a long-term follow-up study". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 2008, *139,* 169.

[23] Bragheto A.M., Caserta N., Bahamondes L., Petta C.A.: "Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging". *Contraception*, 2007, *76*, 195.

[24] Bahamondes L., Espejo-Arce X., Hidalgo M.M., Hidalgo-Regina C., Teatin-Juliato C., Petta C.A.: "A cross-sectional study of the forearm bone density of long-term users of levonorgestrel-releasing intrauterine system". *Hum. Reprod.,* 2006, *21,* 1316.

[25] Magalhães J., Aldrighi J.M., de Lima G.R.: "Uterine volume and menstrual patterns in users of the levonorgestrel-releasing intrauterine system with idiopathic menorrhagia or menorrhagia due to leiomyomas". *Contraception,* 2007, *75*, 193.
[26] Grigorieva V., Chen-Mok M., Tarasova M., Mikhailov A.: "Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas". *Ferti. Steril.,* 2003, *79*.
[27] Möller B., Rönnerdag M., Wang G., Odlind V., Olovsson M.: "Expression of vascular endothelial growth factors and their receptors in human endometrium from women experiencing abnormal bleeding patterns after prolonged use of a levonorgestrel-releasing intrauterine system". *Hum. Reprod*., 2005, *20*, 1410.
[28] www.researchvegf.com
[29] Hague S., Oehler M.K., Mackenzie I.Z., Bicknell R., Rees M.C.: "Protease activated receptor-1 is down regulated by levonorgestrel in endometrial stromal cells". *Angiogenesis*., 2002, *5*, 93.
[30] Laoag-Fernandez J.B., Maruo T., Pakarinen P., Spitz I.M., Johansson E.: "Effects of levonorgestrel-releasing intra-uterine system on the expression of vascular endothelial growth factor and adrenomedullin in the endometrium in adenomyosis". H*um. Reprod*., 2003, *18*, 694.
[31] Royal College of Obstetricians and Gynaecologists (RCOG): "The Management of Menorrhagia in Secondary Care (National Evidence-Based Clinical Guideline No. 5)". London, UK, RCOG Press, 1999.
[32] Soleymani Majd H., El Hamamy E., Chandrasekar R., Ismail L.: "Migration of levonorgestrel IUS in a patient with complex medical problems: what should be done?". *Arch. Gynecol. Obstet*., 2008.
[33] Khan Z.A., Khan S.A., Williams A., Mobb G.E.: "Intravesical migration of levonorgestrel-releasing intrauterine system (LNG-IUS) with calculus formation". *Eur. J. Contracept. Reprod. Health Care,* 2006, *11*, 243.
[34] Steen R., Shapiro K.: "Intrauterine contraceptive devices and risk of pelvic inflammatory disease: standard of care in high STI prevalence settings". *Reprod. Health Matters,* 2004, *12*, 136.
[35] Merki-Feld G.S., Lebeda E., Hogg B., Keller P.J.: "The incidence of actinomyces-like organisms in Papanicolaou-stained smears of copper- and levonorgestrel-releasing intrauterine devices". *Contraception*, 2000, *61*, 365.
[36] FSRH Guidance (November 2007) Intrauterine Contraception.
[37] Backman T., Ilkka R., Sakke H., Markku K.: "Pregnancy during the use of levonorgestrel intrauterine system". *Am. J. Obstet. Gynecol*., 2004, *190*, 50.
[38] Johnson B.A.: "Insertion and removal of intrauterine devices". *Am. Fam. Physician,* 2005, *71*, 95.
[39] Canavan T.P.: "Appropriate use of the intrauterine device". *Am. Fam. Physician,* 1998, *58*, 2077.

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