REVIEW ARTICLE

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Benefit-Risk Assessment of the Levonorgestrel Intrauterine System in Contraception

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Abstract

The levonorgestrel-releasing intrauterine system (IUS) is a long-acting, fully reversible method of contraception. It is one of the most effective forms of contraception available, and combines the advantages of both hormonal and intrauterine contraception. The levonorgestrel-releasing IUS also gives the users many non-contraceptive benefits: the amount of menstrual bleeding and the

number of days of menstrual bleeding are reduced, which makes it suitable for the treatment of menorrhagia (heavy menstrual blood loss). Dysmenorrhoea (painful menstruation) and premenstrual symptoms are also relieved. In addition, the levonorgestrel-releasing IUS provides protection for the endometrium during hormone replacement therapy.

The local release of levonorgestrel into the uterine cavity results in a strong uniform suppression of the endometrial epithelium as the epithelium becomes insensitive to estradiol released from the ovaries. This accounts for the reduction in menstrual blood loss. All possible patterns of bleeding are seen among users of the levonorgestrel-releasing IUS; however, most of the women who experience total amenorrhoea continue to ovulate. The first months of use are often characterised by irregular, scanty bleeding, which in most cases resolves spontaneously. The menstrual pattern and fertility return to normal soon after the levonorgestrel-releasing IUS is removed.

The contraceptive efficacy is high with 5-year failure rates of 0.5–1.1 per 100 users. The absolute number of ectopic pregnancies is low, as is the rate per 1000 users. The levonorgestrel-releasing IUS is equally effective in all age groups and the bodyweight of the user is not associated with failure of the method.

In Western cultures continuance rates among users of the levonorgestrel-releasing IUS are comparable with those of other long-term methods of contraception. Premature removal of the device is most often associated with heavy menstrual bleeding and pain, as with other long-term methods of contraception, and is most common in the youngest age group. When adequately counselled about the benign nature of oligo- or amenorrhoea, most women are very willing to accept life without menstruation. The risk of premature removal can be markedly diminished with good pre-insertion counselling, which also markedly increases user satisfaction. User satisfaction is strongly associated with the information given at the time of the levonorgestrel-releasing IUS insertion. Thus, the benefits of the levonorgestrel-releasing IUS make it a very suitable method of contraception for most women.

The levonorgestrel-releasing intrauterine system (IUS) is an efficient method of contraception with many non-contraceptive benefits. The aim of this article is to evaluate the benefits and risks of this device as a form of contraception to help clinicians put this method of contraception into perspective. In order to achieve this aim the current knowledge of the levonorgestrel-releasing IUS as a contraceptive method has been summarised. Therefore, not all available studies on non-contraceptive indications have been included. Medline was used for the literature search (1966–June 2004) using the keywords: 'levonorgestrel intrauterine system' and 'contraception', 'progestin-only contraception' and 'long term contraception'.

In general, large and comparative studies were preferred for the assessment of levonorgestrel-releasing IUS performance but since there are few randomised studies on contraceptive efficacy, non-comparative studies evaluating the performance in routine clinical use were also included. The mechanism of action is primarily based on early reports on the levonorgestrel-releasing IUS but the latest evidence is included when relevant to the contraceptive efficacy. Numerous articles on the levonorgestrel-releasing IUS have been published; therefore, it is possible that the author's subjectivity may be involved in selecting articles for review and in interpreting their results. Relevant articles were included regardless of the date of publication but no hand searching was carried out. Only articles published in English were included.

1. The Structure of the Levonorgestrel-Releasing Intrauterine System (IUS)

The levonorgestrel-releasing IUS consists of a plain plastic T-shaped white polyethylene frame. The frame is impregnated with barium sulfate, which makes it radio-opaque. The polydimethylsiloxane cylinder releasing levonorgestrel is attached to the vertical arm of the T-frame and covered with a release rate-regulating polydimethylsiloxane membrane. The reservoir contains 52mg of levonorgestrel (or 50% by weight).

The length of the IUS is 32mm, which is also the overall length of the horizontal arms (figure 1).[1] The initial average daily release of progestogen is 20μg. The effective lifespan of the device is 5 years even though efficacy for up to 7 years has been reported.[2]

2. Current Indications for Use

The levonorgestrel-releasing IUS was initially developed as a contraceptive method and it is approved as a contraceptive method in all 101 countries in which it has been launched. The levonorgestrel-releasing IUS can also be used by non-parous women providing that their uterus is of normal size. In some cases local anaesthesia and dilation may be needed during insertion. Intrauterine contraception is not considered to be the first choice for non-parous women. The levonorgestrel-releasing IUS is especially suitable as contraception for premenopausal women as an alternative to sterilisation.

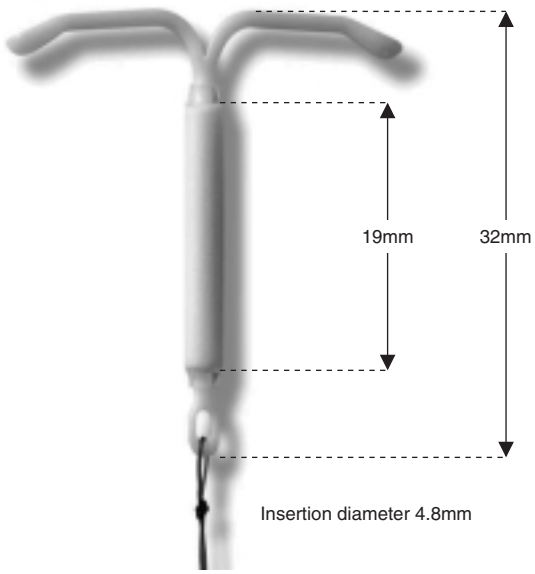

Fig. 1. The structure of the levonorgestrel-releasing intrauterine system (reproduced with permission from Schering OY, Turku, Finland).

The non-contraceptive health benefits on menorrhagia and dysmenorrhoea are indications of use in several countries. Due to the strong suppression of the endometrium by levonorgestrel, the amount of menstrual blood flow is markedly reduced.[3] Even though the levonorgestrel-releasing IUS has not been evaluated as a primary method of treatment for dysmenorrhoea, there are several reports that painful menstruations are improved or eliminated during the use of the levonorgestrel-releasing IUS.[4-6] Furthermore, the relief of dysmenorrhoea has been reported among women who have been treated for menorrhagia with the levonorgestrel-releasing IUS.[7]

The strong, local progesteronic effect of the levonorgestrel-releasing IUS prevents endometrial hyperplasia during hormone replacement therapy,[8-10] which is an approved indication for its use in some countries. Experience from clinical studies covers over 12 000 woman-years and over 60 000 woman-years from studies on routine, clinical practice.

3. Pharmacokinetics

Levonorgestrel released from the IUS is quickly absorbed into the capillary network in the basal membrane of the endometrium and thereby into the systemic circulation.[3] Levonorgestrel is detectable in plasma just 15 minutes after insertion.[11] The maximum plasma levels (175–1589 nmol/L) are reached within hours after insertion.[12] The individual plasma concentrations remain fairly stable during the first weeks but decline with time.[3,4,12] At 3 months after insertion the mean plasma concentrations are 142 ± 46 ng/L and after 48 months of use are 81 ± 22 ng/L.[3] The mean plasma concentrations are between 100 and 200 ng/L.[3] However, there is considerable interindividual variation in levonorgestrel plasma concentrations.[3,12] The concentrations reached with the levonorgestrel-releasing IUS are lower than those reached with the levonorgestrel-releasing implant and progestogen-only pill.[3,4,13-17]

After the first year with the two-rod levonorgestrel implants the mean concentrations of levonorgestrel are 345 ng/L.[14] The circulating levels reached with the levonorgestrel-releasing IUS equal about three progestogen-only pills per week.[18]

In the circulation, levonorgestrel strongly binds to sex hormone-binding globulin (SHBG).[19] Higher levels of both SHBG and levonorgestrel have been detected in women with anovulatory cycles.[12,20]

The levonorgestrel concentrations in the endometrium are very high. The concentrations in the myometrium and in the fallopian tubes are significantly lower than in the endometrium.[3,13,21]

4. Mechanism of Action

It is not possible to demonstrate a single mode of action of the levonorgestrel-releasing IUS. The main factors behind the contraceptive action of the device are scanty cervical mucus and strong suppression of the endometrium.[12,22-25] The local effect of progestogen causes the cervical mucus to thicken.[22,23] The constantly elevated circulating levels of levonorgestrel prevent the normal thinning of cervical mucus at mid-cycle and the cervical mucus remains scanty and viscid as in women treated with levonorgestrel-releasing implants.[24] The changes in the cervical mucus clearly have a strong effect on contraceptive efficacy but research on this effect of the levonorgestrel-releasing IUS is insufficient. Other suggested mechanisms to prevent conception are inhibition of sperm motility and function inside the uterus and in the fallopian tubes preventing fertilisation[25,26] and prevention of endometrial growth.[20,22,27-29] Early studies on the progestogen 2 μg/day device suggest that the contraceptive effect occurs before fertilisation,[26] since neither elevation in the beta human chorionic gonadotropin (βHCG) levels[25] nor fertilised eggs from the reproductive tract have been detected.[24] Even though ovulation is inhibited in some women,[20,21] it is not believed that it has a major effect on contraceptive efficacy. A foreign body effect similar to other intrauterine contraceptive devices is also present.[23,25]

4.1 Endometrial Effects – Hormonal but Local

Even though the levonorgestrel-releasing IUS is a hormonal method of contraception, the main mechanism of action is local in the uterine cavity.[30,31] The concentration of levonorgestrel in the endometrial epithelium is very high and the endometrial concentration is 1000 times higher than the plasma concentration (figure 2).[14]

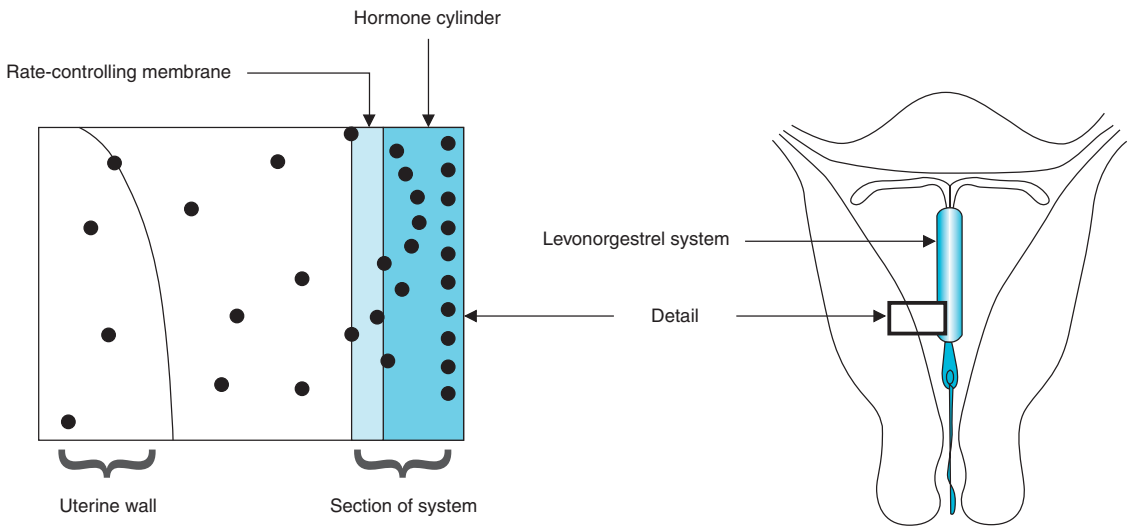

Fig. 2. Mechanism of levonorgestrel release from the intrauterine system (reproduced with permission from Schering OY, Turku, Finland).

The strong effect on endometrial epithelium is considered to be most important to the contraceptive efficacy.[30] High local concentration of levonorgestrel in the endometrial epithelium results in an even and strong suppression of the endometrium, with glandular atrophy, decidualisation of the stroma and inactivation of endometrial cells.[23,25,27,31-34] These typical changes can be seen in the endometrial epithelium 3 months after insertion of the IUS[3,4,23] and they remain unchanged during the use of the system.[23] The foreign body reaction seen with all intrauterine methods of contraception consists of stromal leukocytic infiltrates, which sometimes contain plasma cells.[23,25,32] The morphological changes occur throughout the endometrium and are not limited to the immediate vicinity of the device.[33]

The changes in endometrial epithelium diminish the amount of menstrual bleeding.[3-5,19,34] After removal of the IUS the histology of the endometrium rapidly returns to normal.[23,29,35]

With constantly high concentrations of levonorgestrel in the endometrial cells the cyclic changes in endometrial morphology are lacking.[30] The presence of levonorgestrel in endometrial cells causes high expression of insulin-like growth factor binding protein-1 in the endometrium, which inhibits the activity of insulin-like growth factor-I (IGF-I). IGF-I, on the other hand, is considered to mediate the mitogenic action of estrogens: inhibition of its activity causes suppression of endometrial proliferation.[36] It has also been suggested that the continuous induction of plasminogen activator inhibitor-1 by levonorgestrel could contribute to the therapeutic effect of the IUS on heavy menstrual blood loss.[37]

Glycodelin A messenger RNA and protein expression before and mid-cycle in women using the levonorgestrel-releasing IUS have been described. Possibly this untimely production of glycodelin A adds to the contraceptive action of the levonorgestrel-releasing IUS.[38] This inappropriate production of glycodelin A coincides with the observed down regulation of the progesterone receptor.[39]

4.2 Effects on Ovarian Function

The effects of intrauterine administration on ovarian function are dose-dependent and a daily release of more than 50μg would be needed for complete inhibition of ovulation.[12,20,21,29] With most women the plasma levels of levonorgestrel remain so low that they are not sufficient to prevent ovulation.[12,20,21] It is possible that the low circulating levels of levonorgestrel are sufficient to exert an effect on gonadotrophin secretion and disturb the follicular development in some of the women studied.[39,40] In a study by Jarvela et al.,[41] women with ovarian cysts had higher mean estradiol concentrations than those with normal ovaries. The mean serum levonorgestrel concentration also tended to be higher in women with ovarian cysts.[41] This is in accordance with the theory that the levonorgestrel-releasing IUS may sometimes inhibit ovulation and exert subtle disturbances in hypothalamic-pituitary-ovarian function and thus result in alterations of follicular development and might contribute to the high contraceptive efficacy in addition to the local effect on the endometrium.[39,40]

All patterns of ovarian function have been reported including normal ovulatory cycles, anovulatory cycles with inhibition of estradiol production, anovulatory cycles with high follicular activity and ovulation with inadequate luteal phase.[3,20,21,28,29] Most (85%) users of the levonorgestrel-releasing IUS continue to ovulate.[19-21,35,36]

Since estradiol levels during use of the IUS remain within the range of healthy fertile women without contraception, no effect on, for example, bone metabolism is expected.[40] The estradiol levels show no significant difference between women with ovulatory and anovulatory cycles.[18-21] Missed menstrual bleeding is not sufficient to indicate anovulation and the menstrual bleeding pattern relates neither to plasma levonorgestrel concentrations nor to ovarian function.[11,18,28,29]

5. Contraceptive Efficacy

The introduction of hormonal steroids to IUS devices has combined the favourable effects of intrauterine and combined oral contraception. After determination of the favourable dose of daily release of levonorgestrel, the result has been a system that improves user compliance and convenience and has high contraceptive efficacy.[42] The contraceptive efficacy of the levonorgestrel-releasing IUS is high with a protection against pregnancy comparable to that of female sterilisation.[43-45] The efficacy of oral

Table I. Cumulative pregnancy rates per 100 users at 1, 3 (and 5) years in randomised, clinical studies

Study	Reference method	No. of women using LNG IUS (reference)	1-year rate of LNG IUS	1-year rate of reference method	3-year rate of LNG IUS	3-year rate of reference method	5-year rate of LNG IUS	5-year rate of reference method
Sivin et al.[45]	CuT 380Ag	1124 (1121)	0.2	0.3	0.4	1.0	1.1	1.4
ICMR[49]	CuT 380Ag	475 (434)	0.0	0.8	0.0	1.0		
ICMR[49]	CuT 220B	475 (500)	0.0	0.9	0.0	1.6		
ICMR[49]	CuT 220C	475 (496)	0.0	0.0	0.0	0.3		
Andersson et al.[44]	NovaT®	1821 (937)	0.1	1.0	0.3	3.7	0.5	5.9
Gao et al.[55]	Norplant II	100 (100)	1.0	0.0				
Wang et al.[56]a	Norplant II	100 (100)			1.0	0.0		
Cox et al.[53]		678	0.6		1.0		1.0	

a Extension of earlier study.

ICMR = Indian Council of Medical Research; **LNG IUS** = levonorgestrel-releasing intrauterine system.

combined pills is excellent in optimal use but the efficacy is often compromised by compliance difficulties.[46,47] The effective lifetime of an intrauterine contraceptive method is long and the efficacy is not compromised by user failures. Sterilisation, even though highly effective, is an irreversible method with no positive effects on either menstrual blood flow or pain related to menstruation.[48]

Pregnancy rates in the randomised studies on the levonorgestrel-releasing IUS, as with other long-term contraceptive methods, have been very low and there are several studies in which there were no pregnancies in the levonorgestrel-releasing IUS group.[4,49-52] Non-comparative studies evaluating the performance of the levonorgestrel-releasing IUS in routine, clinical practice have also reported fairly low pregnancy rates.[53,54] The pregnancy rates per 100 users in comparative and non-comparative studies are presented in table I.

Some studies have shown higher failure rates with other long-acting contraceptive methods in younger age groups. The failure rates with NovaT® [1] decrease with patient age[57] and with progestogen-only oral contraception failure rates have consistently shown a strong negative correlation with age. In the Oxford study, the Pearl rates (pregnancies per 100 woman-years) for women aged 25–29 years were 21 compared with 0.3 for women over 40 years.[58] With progestogen-releasing implants failure rates have been shown to increase with increasing bodyweight.[16,17,58] In a 5-year study on levonorgestrel-releasing implants, all accidental pregnancies occurred in heavier women.[16] The levonorgestrel-releasing IUS has been equally effective in all age groups and the weight of the user is not associated with contraceptive efficacy.[4,44,45,55,56]

Clinical experience with pregnancies in women using a levonorgestrel-releasing IUS is virtually non-existent[59] because such occurrences are rare due to low pregnancy rates. Since it is well established that women becoming pregnant with an intrauterine device (IUD) in place are at greatly increased risk for spontaneous abortion,[60] a consensus among clinical practitioners has been to remove the IUD as soon as the pregnancy has been recognised.[60] This also applies to the levonorgestrel-releasing IUS.[59] If the IUD is expelled or removed shortly after conception, the incidence of spontaneous abortion is significantly reduced.[61]

5.1 Ectopic Pregnancy

The risk of ectopic pregnancy among women using a copper-releasing CuT 380Ag is lower than the risk among sexually active women using no contraception.[62,63] Nevertheless, it is widely believed that ectopic pregnancies are more common among users of an IUD. IUDs, like all contraceptive methods, decrease both the risk of intrauterine and extrauterine pregnancy.[62-64] Since all IUDs are more effective in preventing intrauterine than

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ectopic pregnancy, the probability of an ectopic pregnancy is increased in the case of a pregnancy beginning during the use of an IUD.[62,63] The strong local effect of levonorgestrel on the endometrium accounts for its high contraceptive efficacy against intrauterine pregnancy.[3,44,45] Therefore, in the rare case of a pregnancy beginning during the use of the levonorgestrel-releasing IUS, it is highly likely to be ectopic.[18]

The ectopic pregnancy risk among women not using contraception has been estimated to be 0.12–0.26 per 100 woman years.[65] When this estimate is compared with the rate of ectopic pregnancy in users of the levonorgestrel-releasing IUS from the comparative trials (0.02 per 100 woman years),[4,44,45] the levonorgestrel-releasing IUS can be considered to give a major reduction in the risk of ectopic pregnancy.[18]

The ectopic pregnancy rates with the levonorgestrel-releasing implants have been 0.03 and 0.04 per 100 users over 5 years.[16,24] In the Population Council Study[45] none of the six pregnancies among 1124 users of the levonorgestrel-releasing IUS were ectopic. In the group of women using a CuT 380Ag IUD there were ten pregnancies, of which two were ectopic, giving the 5-year ectopic rate of 6 per 100 users. In the study by Andersson et al.,[44] one of the five pregnancies among the 1821 users of the levonorgestrel-releasing IUS was ectopic compared with seven out of 35 pregnancies with the NovaT®. Since two of the five pregnancies with the levonorgestrel-releasing IUS were due to an unnoticed expulsion, one in three pregnancies with the levonorgestrel-releasing IUS *in situ* was ectopic. Case reports of tubal, ovarian and cervical pregnancies during the use of the levonorgestrel-releasing IUS have been published.[66-69] It is mandatory to take a pregnancy test and keep the possibility of an ectopic pregnancy in mind if the settled menstrual pattern changes during the use of the levonorgestrel-releasing IUS or symptoms typical of pregnancy occur.

5.2 Expulsion

Progestogens were first placed into intrauterine contraceptive devices to reduce uterine contractions and, consequently, the risk of expulsion during the use of the IUS.[70] Study findings do not suggest any difference between the expulsion rates of the levonorgestrel-releasing IUS and copper-releasing IUDs.[44,45] In the Population Council Study,[45] the expulsion rates for the levonorgestrel-releasing IUS (11.7 per 100 users) were higher than those for copper-releasing IUDs (8.3 per 100 users). In the European study,[44] the expulsion rates were 5.8 and 6.7, respectively. In some studies the expulsion rate has been higher with the levonorgestrel-releasing IUS during the first year of use,[4] while in others expulsions have occurred at a fairly constant rate.[52,53,71] In studies on different copper-releasing IUDs the time of the expulsion has varied.[57,72] In a Brazilian study, the expulsion rates with the levonorgestrel-releasing IUS were significantly higher in women who used the system because of heavy bleeding.[73] With NovaT® the expulsion rates have not had a clear correlation with age or parity but with other copper-releasing IUDs the expulsion rates have been higher in younger age groups and among nulliparous women.[57] Postpartum IUD insertions have also been associated with a higher expulsion rate.[74] The expulsions with the levonorgestrel-releasing IUS have mostly occurred during the first 2 years of use.[44,45]

A pregnancy due to an unnoticed expulsion of the levonorgestrel-releasing IUS is a real but rare occurrence. In the Scandinavian study, two out of the five pregnancies in the levonorgestrel-releasing IUS group occurred due to an unnoticed expulsion.[44] In the Brazilian study, there was one pregnancy at the 15th month of use due to an unnoticed expulsion.[74]

5.3 Return of Fertility After Removal of the Levonorgestrel-Releasing IUS

Many couples tend to postpone their childbearing and so use contraception for many years. Therefore, it is of utmost important that the chosen contraceptive method is efficient during administration but does not reduce fertility when discontinued. It has been proposed that the intrauterine methods of contraception increase the risk of tubal infertility.[75]

In a European multicentre clinical trial the fecundicity of former users of the levonorgestrel-releasing IUS and the copper-releasing NovaT® was compared after the IUD was removed by women wanting to become pregnant.[76] The two groups were similar in age, parity, history of pelvic inflammatory disease (PID) and the duration of use of the

IUD. Even though the levonorgestrel-releasing IUS has a strong suppressive effect on the endometrium, the pregnancy rates have been similar to pregnancy rates following the removal of other long-acting contraceptive methods (copper-releasing IUDs, levonorgestrel-releasing implants) and also to pregnancy rates for women without contraception.[75-79] In one of the first studies on fertility after discontinuation of the levonorgestrel-releasing IUS, 19 of 21 women conceived during the first month.[76]

During the follow-up period of 2 years, 75% of the former users of the levonorgestrel-releasing IUS and 70% of the former users of the NovaT® became pregnant. Of those who conceived, 92% in both groups became pregnant during the first year. The pregnancy rates are similar for prior users of the levonorgestrel-releasing IUS and NovaT®,[76,79] as well as the CuT 380Ag device[78] and the levonorgestrel-releasing implant.[77]

Belhadj et al.[78] followed 110 women who discontinued the use of either the CuT 380Ag or levonorgestrel-releasing IUS due to a wish to become pregnant. In both groups the first year pregnancy rate was >90%. In the women with oligo- or amenorrhoea, the fecundicity was lower during the first month after the removal but the pregnancy rates within 1 and 2 years were similar to prior users of other methods of contraception. After removal of the NovaT® and the levonorgestrel-releasing IUS the pregnancy rates at 1 year after the removal were 77% and 88%, respectively,[76] and there was no difference in the outcome of pregnancies between the prior users of NovaT®, CuT 380Ag, the levonorgestrel-releasing IUS or Norplant® capsules.[76,77] The majority of pregnancies after removal of the levonorgestrel-releasing IUS have been carried to term and all children were reported as healthy and normal.[76-79] However, Doll et al.[80] have suggested that prolonged use of intrauterine contraception might be associated with lower fertility rates.

6. Safety Issues

6.1 Insertion Difficulties and Perforation

Proper training in insertion technique of the levonorgestrel-releasing IUS is a prerequisite for successful performance of the system.[81-83] Good fundal placement in the uterine cavity is particularly important with this device.[82] Because the insertion technique is different from other IUDs, special emphasis should be given to training in the correct technique.[81-83] As with any minor surgical procedure, insertion and removal technique is best learned through directly supervised training.[83] The insertion instrument has recently been changed to allow a simple one-handed technique. The levonorgestrel-releasing IUS is inserted within the first 10 days of the menstrual cycle, no later than 5 days from the last day of bleeding, regardless of indication.[82] When a levonorgestrel-releasing IUS is replaced with a new one the insertion can be done immediately after removal of the previous system regardless of the day of the cycle.[81,82]

Some problems with the insertion of the levonorgestrel-releasing IUS can be expected since the outside diameter of the insertion tube is, due to the levonorgestrel-containing reservoir, 1mm wider than the insertion tube of the commonly used copper-releasing IUDs.[82] If necessary, paracervical local anaesthesia and dilation of the cervical canal to 5mm can be carried out. Vaginal or oral misoprostol could reduce the need for paracervical block.[82]

In a study by Sivin et al.,[84] 11.3% of the insertions were described as difficult. British researchers reported 11% of fittings as difficult with no relationship to the ease of fitting and parity, status of fitter, interval since pregnancy or breast feeding. In this study, 14% needed dilation and, of these, 93 cases (30%) were reported as difficult. Surprisingly, only 4% of the insertion difficulties were reported in the under 25 years age group but in 14% of the 30–34 years age group.[53] A recent Finnish study underlines the importance of pain relief for young nulliparous women since moderate to severe pain at insertion was experienced by 58.5% of the nulliparous women compared to 18.6% among the parous women. When good pain relief is taken care of, the levonorgestrel-releasing IUS can be considered suitable even for young nulliparous women.[85] There also seems to be a learning curve in the insertion of the levonorgestrel-releasing IUS since more insertion difficulties were reported among the first insertions by the physician.[86] In a Finnish study on Norplant® insertions, 9% of the women mentioned

problems with Norplant® insertion and one-third reported problems with removal.[87] The insertion and removal problems with the new implants were less frequent.[16,88]

In a study of long-term use of the levonorgestrel-releasing IUS, the proportion of insertions in which local anaesthesia was needed increased from 6% at the insertion of the second IUS to 13% at the insertion of a third one. It is not clear whether the increase in the insertion difficulties is related to the increased age of the women or the number of insertions. No correlation between difficult insertion and previous conisation was noted.[89]

The most serious complication of an intrauterine contraceptive device is uterine perforation – the incidence of which has been estimated to be 0–1.3 perforations per 1000 insertions.[90] The perforation is usually asymptomatic but in rare cases can cause severe morbidity. In cases of a perforation it has been customary to remove the misplaced IUD,[91] although recently expectant management has been recommended to reduce the morbidity caused by the removal operation.[92] Haimov-Kochman et al.[92] have studied the adhesion-forming potential of a misplaced levonorgestrel-releasing IUS. Since the adhesion-forming potential seems to be low, they suggest that the conservative approach could be acceptable for asymptomatic patients.

The levonorgestrel-releasing IUS can be inserted right after a medical abortion[93] and 6 weeks after delivery.[94] Special care should be taken with postpartum insertion of the levonorgestrel-releasing IUS since perforation of the uterus have been reported even by the experienced inserters and lactating women are seen to be a risk group for perforation.[90,94] If the strings of an IUS are not visible, attempts should be made to locate the device by transvaginal sonography, x-ray or hysteroscopy, but it should be kept in mind that perforation may have occurred even if the strings are visible.[95] Since the levonorgestrel-releasing IUS alters the bleeding pattern with most women, expulsion or perforation should be suspected if a woman fitted with a levonorgestrel-releasing IUS experiences a completely normal menstrual pattern.[90]

6.2 Infections

Pelvic infection is a much feared and misunderstood condition. PID leading to tubal occlusion and infertility has been blamed on IUD use.[63,96,97] In a recent study by Tsanadis et al.,[98] there were no PIDs during the study period of 36 months among 200 women. Other recent studies have made it increasingly clear that an increased risk of PID among women with an IUD is strongly associated with behavioural factors, such as an increased number of sexual partners.[63,75,99,100] The risk of infection is concentrated in the first month after insertion, subsequently the risk is comparable to that in non-IUD users.[2,63,98-100] The subsequent risk of infections is related to sexually transmitted organisms, such as chlamydia.[63] Therefore, care in selection of candidates for the use of any IUD and avoiding insertion in persons at high risk for sexually transmitted disease should minimise the occurrence of PID in women using IUDs.[63,75,97,100] To further reduce the risk of infection in relation to the insertion, all underlying vaginal and cervical infections should be treated before insertion.[43,82] Due to long-term effectiveness, the levonorgestrel-releasing IUS needs to be replaced very infrequently thus making an increased risk of infection minimal. The levonorgestrel-releasing IUS, as with the levonorgestrel-releasing implant,[24,101] makes the cervical mucus thicker and more difficult to penetrate, which has been suggested to be associated with lower infection rates.[23] In the study by Andersson et al.,[44] the removal rates for PID were 0.8 and 2.2 for the levonorgestrel-releasing IUS and NovaT® users, respectively. The difference was greatest in the youngest age group, among women under 25 years of age. In the Indian Council of Medical Research (IMCR) study, the rates for PID per 100 women were 0.8 and 1.5 for the CuT 380Ag and levonorgestrel-releasing IUS, respectively.[49] In the study by the Population Council, the rates were equal in both the copper-releasing IUD and levonorgestrel-releasing IUS groups.[45] However, it is possible that the women participating in clinical trials are selected due to a low risk risk of sexually transmitted disease.

Actinomyces infections have often been associated with the use of an IUD. The relationship between actinomyces in the Pap smear of asymptomatic IUD

users and the eventual development of pelvic actinomycosis is unclear.[102] Actinomyces species are normal inhabitants of the human gastrointestinal tract and genital tract.[102,103] Even though many authors recommend the removal of an IUD and/or an antibiotic treatment when actinomyces-like organisms have been detected in a Pap smear,[104] Fiorino considers, based on an extensive review of the literature, that currently neither removal nor antibacterials are indicated for an asymptomatic patient with an incidental finding of actinomyces on routine cervical smear.[102] In a study by Merki-Feld et al.,[104] the incidence of actinomyces-like organisms in Pap smears of levonorgestrel-releasing IUS users seems lower than with other types of IUDs.

To determine whether the levonorgestrel-releasing IUS has a protective effect on infections (as has been suggested by Toivonen et al.[43]) a large sample of women in a normal clinical setting should be examined.

6.3 Metabolic Effects

Due to the low daily release and low plasma concentrations of levonorgestrel, the systemic steroidal effects are minimal.[44,45] There seems to be no significant change in carbohydrate metabolism, systemic coagulation parameters, liver enzymes or serum lipid levels.[3,13,105,106] The blood glucose, serum insulin and serum total testosterone concentrations remain on the initial level and are similar with both the users of the levonorgestrel-releasing IUS and copper-releasing IUD.[107] When the users of the levonorgestrel-releasing IUS were followed for 12 years, only a slight, non-significant increase in blood pressure was observed.[89] The bodyweight was similar compared with users of the copper-releasing IUD, with an equal gain in bodyweight indicating that a slight increase in weight occurs with ageing.[89]

6.4 Functional Ovarian Cysts

An increased incidence of functional ovarian cysts is associated with all progestogen-only methods of contraception.[59,108] The follicular cysts are more common in users of Norplant® than in women with normal cycles but rarely present with complications.[24,108] With progestogen-only pills, functional cysts in eight of 21 progestogen-only pill users were reported.[109]

The increased incidence of functional ovarian cysts has also been observed in users of the levonorgestrel-releasing IUS. Robinson et al.[110] observed that six of 50 women (12%) developed functional ovarian cysts between 6 weeks and 12 months after insertion. In the randomised study by Andersson et al.,[44] three IUSs were removed due to ovarian cysts, but the overall incidence was not reported. The clinically diagnosed rate reported by the Population Council was 1.2 per 100 woman-years compared with 0.4 per 100 woman-years with the copper-releasing IUD users.[45] Jarvela et al.[41] observed ovarian cysts in 31% of the study subjects after 3 months of insertion of the levonorgestrel-releasing IUS. All the cysts disappeared spontaneously during the 3–4 month follow-up with the levonorgestrel-releasing IUS *in situ*. Progestogen-related cysts most often resolve spontaneously and should therefore be managed conservatively.[18,59] In the absence of complications, no specific intervention is indicated.[18,40,41,110]

6.5 Effect on Breast-Feeding and Lactation

All steroid hormones pass into breast milk and have the potential to reach the infant.[111] In most studies, the duration of the breast-feeding period and the weight gain in infants of mothers using oral progestogen-only pills were similar to those in infants of mothers using non-hormonal contraception.[112-114] In a large study conducted by the WHO of 2466 nursing mothers either using the progestogen-only method (levonorgestrel implants, progesterone-only oral contraceptive pills, depo medroxyprogesterone or injectable norethisterone) or a non-hormonal alternative showed no consistent differences in infant growth or development during the first year between the groups using either hormonal or non-hormonal contraception.[115,116]

With the levonorgestrel-releasing IUS the concentrations of levonorgestrel in milk are detectable but very low.[94,117] In a study by Heikkilä et al.[117] the duration of lactation with the levonorgestrel-releasing IUS users was slightly shorter than in the NovaT® group. The weight gain and growth of the infants were similar at 1 year of age. No difference

was detected in liver enzymes, serum proteins, lipids or haemoglobin levels in the infants.

6.6 Teratogenic or Carcinogenic Effects

Due to the good contraceptive efficacy of the levonorgestrel-releasing IUS,[44,45] there is virtually no experience of pregnancies with the levonorgestrel-releasing IUS in place for either part of or throughout the pregnancy. Any intrauterine contraceptive method *in situ* after the first trimester has been associated with an increased risk of miscarriage, fetal loss and preterm labour and delivery.[60] If a pregnancy begins with an IUD *in situ*, either the levonorgestrel-releasing IUS or copper-releasing IUD, the intrauterine contraceptive device should be removed.[60,61] Hypothetically, the androgenicity of levonorgestrel may implicate a risk to the fetus. Healthy babies have been born to mothers with extremely high circulating levels of androgens[118] and it has been suggested that the placental aromatase system provides a relatively large safety margin in protecting the female fetus from the masculinising effect of high maternal circulating androgens and the well-being of the fetus is not otherwise compromised.[118,119]

7. Change in Bleeding Pattern

After the insertion of an IUD the bleeding pattern usually changes. The changes in bleeding pattern are the most important adverse effects leading to premature removal of the intrauterine contraceptive device.[44,45,57,73,83] The menstrual bleeding often becomes scanty following the insertion of the levonorgestrel-releasing IUS. Intermenstrual bleeding and spotting are common in the first months but gradually decrease by the 6th month.[44,120] During the first month after insertion there are significantly more days of bleeding and spotting with the users of the levonorgestrel-releasing IUS compared with the copper-releasing IUD.[44] With the copper-releasing IUD the pattern of bleeding after the insertion is established early and after the first month, the number of days of bleeding rapidly settle around 5.[120] With the levonorgestrel-releasing IUS the number of bleeding days decreases with each passing month. By the 6th month the number of days of spotting and bleeding are less than with the users of the copper-releasing IUD.[44,120,121] Any pattern of menstruation is possible with users of the levonorgestrel-releasing IUS. In a study of 14 women using the levonorgestrel-releasing IUS for 6 years, five women had normal menstrual cycles, seven had prolonged or irregular cycles and two were amenorrheic.[28] Immediate postabortal insertions have been associated with slightly better patterns of bleeding than postmenstrual insertion.[120]

The amount of blood lost with the levonorgestrel-releasing IUS is gradually decreased. After 6 months many women have no bleeding: in the Finnish study one-third of women had no bleeding,[48] and in the Brazilian study 44% of women reported amenorrhoea at the 6th month of the study.[73] In a study from Austria, 56% experienced an absence of menstruation, either completely from the time of insertion (47%) or temporarily (9%).[122]

Heavy, excessive bleedings have been reported to continue even with the use of the levonorgestrel-releasing IUS in about 8% of users.[123] With ongoing excessive menstrual bleedings it is worth remembering that endometrial polyps and myoma can be the explanation.[124] Therefore, ultrasound examinations and endometrial biopsies are recommended for continuous bleeding problems. The levonorgestrel-releasing IUS reduces menstrual blood flow by up to 97%.[125-127] The menstrual blood loss is reduced in over 80% of women with confirmed menorrhagia.[127]

7.1 Amenorrhoea Associated with Contraception

Surveys carried out in the 1970s and 1980s suggested that most women preferred regular menstrual bleedings over amenorrhoea.[128] Hence, the development of oral contraceptives have aimed for regular monthly bleedings. Even though it is safe and simple to eliminate menstruation with oral contraceptives, monthly menses still continue to be the standard for most women.[129]

There is no medical advantage to menstruation *per se*. On the contrary, morbidity associated with menstruation is impressive.[128] At minimum, menstruation is a nuisance but in many cases menstruation-related costs constitute a significant expense to the individual, the healthcare system and the sur-

rounding environment. Menstrual dysfunction is one of the most common reasons for which a woman consults her general practitioner.[130] In some countries up to 20% of women will undergo hysterectomy for excessive bleeding.[131]

Several studies suggest that women are actually ready to welcome methods inducing amenorrhoea and 80% of women prefer a change to lighter, shorter or less painful menstrual bleeding.[128,132] Given a choice, over half of women would choose to have their menstruation less often than once a month in both developed and developing countries.[128] In a recent 3-year study, amenorrhoea was considered as a positive change by 81% of women.[122] Women with regular or prolonged bleeding have been found to be more likely to discontinue their method of contraception than those with delayed bleedings or amenorrhoea.[132]

Due to the strong endometrial effect, several users of the levonorgestrel-releasing IUS experience loss of menstrual bleeding after the first 6 months of use.[37,44,45,73,120] In the early studies on the levonorgestrel-releasing IUS, amenorrhoea was a fairly frequent reason for premature removal of the levonorgestrel-releasing IUS indicating that even the providers were uncertain of the benign nature of amenorrhoea induced by the levonorgestrel-releasing IUS. The removal rates due to amenorrhoea varied from six to 19.7 per 100 woman-years.[44,45] With increased information for both the providers and the consumers amenorrhoea has become an accepted and even preferred state by the users. Finnish women who experienced loss of menstrual bleeding during the use of the levonorgestrel-releasing IUS were more likely to continue use of the levonorgestrel-releasing IUS (relative risk 0.46, 95% CI 0.46, 0.50).[123] Discontinuation due to amenorrhoea has been a major source of discontent with the levonorgestrel-releasing IUS in the developing world.[44,49] Since women, both in the developing and developed world, would prefer lighter bleeding less often than once a month[128] it seems safe to assume that with good pre-insertion counselling discontinuation rates due to amenorrhoea could also be diminished in the developing world. Good counselling at the time of accepting a contraceptive method and reassurance during its use is necessary to reduce discontinuation due to bleeding irregularities.[133]

8. Continuation Rates, User Satisfaction and Counselling

Continuous use of a contraceptive method can be considered to be the ultimate measure of user satisfaction[134] and user satisfaction is often presented as continuance rates. When a woman is concerned about the potential adverse effects or safety of the contraceptive method in use, she will simply stop using a perfectly safe and effective method of contraception and possibly will choose a less effective method or decide not to use contraception at all.[47,135-138]

8.1 Continuation Rates

The continuance rates in randomised comparative trials with all the reversible, long-acting methods of contraception have been uniformly good even though the continuation rates in developing countries are lower than with control regimens and than in the Western world.[45,138-141] The 5-year continuance rates with the levonorgestrel-releasing IUS have varied from 33 to 53 per 100 users compared with 40.6 to 50 with the copper-releasing IUDs.[4,44,45] The 1-year continuance rates with levonorgestrel-releasing implants have ranged from 76% to 95%[45,139] and the 5-year rates from 40% to 90%.[17,139]

Recent studies reporting clinical performance of the levonorgestrel-releasing IUS in routine use have shown similar or even better continuance.[53,123] In an epidemiological study of 17 360 women the 1-, 2-, 3-, 4-, and 5-year continuance rates were 93, 87, 81, 75 and 65%, respectively.[123]

Discontinuation rates with the levonorgestrel-releasing IUS, as with other long-acting contraceptive methods, decrease with age.[44,45,123,139,141] Continuous rates are not associated with the previous methods of contraception, parity or socio-economic status.[123,142] The continuation rates from comparative and non-comparative studies carried out for 5 years are presented in table II.

8.2 Counselling and User Satisfaction

Knowledge of the personal experience, acceptance and satisfaction of users is important if the selection of a long-term contraceptive is to meet individual needs.[140] With careful pre-insertion

Table II. Continuation rates of the levonorgestrel-releasing intrauterine system (LNG IUS) and reference methods in comparative and non-comparative studies

Reference	Duration of study (years)	Reference method	No. of women LNG IUS (reference)	Continuance of LNG IUS per 100 users	Continuance of reference per 100 users
ICMR[49]	1	CuT 200B/CuT 200C	475 (500/496)	75.5	82.4/84.4
ICMR[49]a	3	CuT 200B/CuT 200C	473 (500/496)	38.8	45.4/45.4
Luukkainen et al.[143]	1	NovaT®	1821 (937)	79.7	82.2
Toivonen et al.[43]	3	NovaT®	1821 (937)	57.0	59.0
Andersson et al.[44]	5	NovaT®	1821 (937)	46.9	44.5
Sivin et al.[84]	1	CuT 380Ag	755 (754)	75.0	78.0
Sivin et al.[144]a	2	CuT 380Ag	1124 (1120)	59.4	67.5
Sivin et al.[45]a	5	CuT 380Ag	1124 (1121)	33.0	40.6
Sivin et al.[2]a	7	CuT 380Ag	897 (896)	24.9	29.4
Cox et al.[53]a	5		692		

a Extension to earlier study.

ICMR = Indian Council of Medical Research.

counselling, compliance, continuation and patient satisfaction can be increased.[145,146] User satisfaction with the levonorgestrel-releasing IUS is clearly enhanced by careful counselling.[142,145,146] Pre-insertion and continued post-insertional counselling of long-term contraceptive methods should address all advantages and disadvantages of the method, including discussion of the expected adverse events with an emphasis on bleeding disturbances.[142,145-147]

Since the menstrual pattern is likely to be radically altered during the use of the levonorgestrel-releasing IUS[3-5,44] it is essential to counsel women about the early bleeding problems including the possibility of oligo- or amenorrhoea. Counselling about the possibility of oligo- or amenorrhoea has been considered to be very important as it will help women to persevere so that they can enjoy the longer-term benefits.[53]

The majority of women using copper-releasing IUDs, progestogen-releasing implants or levonorgestrel-releasing IUSs are satisfied with their method of contraception.[84,137,140,142,146] Of the users of the levonorgestrel-releasing IUS over 70% have been satisfied with the device.[122,146] Over 70% report to be more satisfied with the levonorgestrel-releasing IUS than with their previous method of contraception, even though over 70% of them reported that one of the reasons for choosing the levonorgestrel-releasing IUS was dissatisfaction with the prior method of contraception.[146] However, prior method of contraception is not associated with user satisfaction on the levonorgestrel-releasing IUS.[142,146] Furthermore, the proportion of satisfied users increases with time of use.[122,146]

8.3 Adverse Effects and Associated Discontinuation

The most common adverse effects leading to discontinuation of use of an intrauterine method of contraception are bleeding disorders and pain.[4,13,14,38,44,45,52,56,71,121,123] The pattern of bleeding problems with the levonorgestrel-releasing IUS are significantly different from those among women using copper-releasing IUDs.[48,49,148] The users of copper-releasing IUDs experience heavy and long-lasting bleedings more often than the users of the levonorgestrel-releasing IUS.[4,44,45]

Approximately 8% of women using the levonorgestrel-releasing IUS report excessive menstrual bleeding during the use of the device. These women had a risk ratio of 2.77 (95% CI 2.51, 3.07) for premature removal of the IUS.[123]

Symptoms that can be considered to be due to circulating levels of levonorgestrel are very common. Therefore, it is often difficult, if not impossible, to determine which symptoms are actually drug related.[147] As the levonorgestrel-releasing IUS is a progestogen-only method of contraception, the hormonal adverse effects expected are similar to other progesterone-only methods. Due to the slow release

Table III. Cumulative discontinuation rates by indication per 100 users after 60 months of use

Study	No. of users	Pregnancy	Expulsion	Bleeding	Pain	Amenorrhoea	Hormonal	Continuation
Andersson et al.[44]	1821	0.5	5.8	13.7	5.9	6.0	12.1	46.9
Sivin et al.[45]	1124	1.1	11.8	15.4[a]		19.7	Not reported	33.0
Cox et al.[53]	692	1.0	5.9	16.7	4.3		20.8[b]	39.6

a Presented as a combined figure for bleeding and pain.

b Including 26 removals due to oligo- or amenorrhoea.

rate of 20μg/day, the plasma concentrations of levonorgestrel with the levonorgestrel-releasing IUS remain lower than with other progesterone-only methods.[18] The possibly hormone-related symptoms are often reported by both the users of the levonorgestrel-releasing implants and users of the levonorgestrel-releasing IUS but they seldom lead to premature removal of either device.[43,52,53,57,124,136] Yet, the hormonal adverse effects are the cause of premature removal of the levonorgestrel-releasing IUS more often than the copper-releasing IUD. The discontinuation rates due to hormonal adverse effects reported by Andersson et al.[44] were 12.1 per 100 users of the levonorgestrel-releasing IUS compared with 2.0 per 100 users of the NovaT®. In a 3-year study of 161 women, only five women had their levonorgestrel-releasing IUS removed due to undesirable adverse effects.[122]

The hormonal adverse effects most commonly reported during the use of the levonorgestrel-releasing IUS are breast tenderness, mood changes and acne. Other hormonal symptoms reported include excessive hairiness or loss of hair, swelling of the lower abdomen and headache.[53] These symptoms are mostly reported during the first months of use.[4-6,44] Many women choosing a hormonal contraceptive method are concerned about weight gain. In a 12-year follow-up study the weight gain was identical among the users of both the copper-releasing IUD and the levonorgestrel-releasing IUS.[89] Reasons for discontinuation are presented in table III.

9. Cost Effectiveness

The cost of an unintended pregnancy is substantial and contraception, regardless of the method, saves money.[149,150] Long-acting methods with high contraceptive efficacy and good continuance rates become extremely cost effective over time. Male and female sterilisation, although having high initial cost, become cost effective over time for those who desire no more children. Sterilisation requires operating room facilities, with potential risks related to anaesthesia and the procedure itself.[47,149,150]

The CuT 380Ag is the most cost-effective reversible contraceptive method available.[149,150] The levonorgestrel-releasing IUS has been shown to be highly cost effective in the treatment of menorrhagia over hysterectomy even in 5-year follow-up.[151,152] Long lifespan, high continuation rates and very high effectiveness make the levonorgestrel-releasing IUS a cost-effective method of contraception, despite the fairly high initial financial outlay of €164 (2004).[153] When the potential savings resulting from the health benefits of the levonorgestrel-releasing IUS (i.e. reduction in the need of sanitary pads due to reduced menstrual bleeding) are taken into account the cost effectiveness is further increased. Chiou et al.[149] estimated that the levonorgestrel-releasing IUS and the CuT 380Ag IUD dominated all methods reviewed (cervical cap, diaphragm, female condom, 3-month injectable, oral contraceptive and spermicide) with the exception of sterilisation. They also considered that these methods have very similar cost effectiveness.

10. Non-Contraceptive Benefits of the Levonorgestrel-Releasing IUS

10.1 Reduction of Menstrual Blood Loss

Menorrhagia is a common problem for which women seek gynaecological consultation.[130] After often unsuccessful medical treatments, a significant proportion of these women will undergo hysterectomy, the incidence of which has been rising.[131,154] Even though hysterectomy can be considered more effective than any other treatment modality of men-

orrhagia,[155] the associated morbidity and costs to society can not be ignored.[155,156] The levonorgestrel-releasing IUS has been at least as effective as the reference medication (tranexamic acid, flurbiprofen, norethisterone, NSAIDs) in reducing menstrual blood loss.[151] When compared with norethisterone, the levonorgestrel-releasing IUS provided an equally effective treatment for menorrhagia with higher user satisfaction and continuance with treatment in the levonorgestrel-releasing IUS group.[157] Comparison with the transcervical resection of the endometrium has showed dramatic effect on bleeding intensity with both methods. Transcervical resection is an operative procedure with uncertain effect on fertility.[158-160] With the levonorgestrel-releasing IUS menorrhagia can be efficiently cured without compromising future fertility, which makes it possible to cure younger patients experiencing menorrhagia who still want to preserve their fertility. The contraception, on the other hand, is efficiently taken care of when it is needed. Hurskainen et al.[155] showed that the health-related quality of life significantly improved during the treatment of menorrhagia with the levonorgestrel-releasing IUS. The system was also found to be a cost-effective alternative to hysterectomy in the treatment of menorrhagia. In a systematic review, Marjoribanks et al.[161] concluded that surgery reduces menstrual bleeding more than medical treatments at 1 year, but the levonorgestrel-releasing IUS appears equally beneficial in improving quality of life and may control bleeding as effectively as conservative surgery over the long term, whereas oral medication suits a minority of women long term.

10.2 Dysmenorrhoea and Premenstrual Syndrome

Menstrual pain can be relieved by prostaglandin antagonists, such as NSAIDs. Combined oral contraceptives often reduce symptoms. The users of the levonorgestrel-releasing IUS have their device removed prematurely due to abdominal pain less often than users of the copper-releasing IUD.[44] The levonorgestrel-releasing IUS reduces dysmenorrhoea and premenstrual syndromes,[49,162] including the reduction of dysmenorrhoea in women who have had the IUS inserted due to menorrhagia. Out of fifty women, 56% reported improvement or even cure in their symptoms premenstrually and dysmenorrhoea was relieved with 80% of them.[162] Still, pain, together with menstrual disturbances, remains the leading cause for premature removal of the levonorgestrel-releasing IUS.[44,45,123]

The levonorgestrel-releasing IUS has also been shown to relieve pelvic pain caused by endometriosis even though the endometriotic foci diminish only slightly.[163,164] Promising results have been published on reduction of blood loss and pain in menorrhagia associated with adenomyosis.[165,166]

10.3 Treatment of Endometrial Hyperplasia and Polyps

Systemic progesterone has been found useful in the treatment of endometrial hyperplasia.[167] Early studies on Progestasert® showed that it completely suppressed endometrial hyperplasia in >80% of cases but after removal the recurrence rate was 36%.[167] A small study on the levonorgestrel-releasing IUS found a more uniform degree of endometrial suppression,[168] which might solve the problem of recurrence after removal. Long-term studies are still needed to confirm the effectiveness of the device on the treatment of endometrial hyperplasia. Still, both the earlier and more recent study authors consider the levonorgestrel-releasing IUS to be a suitable treatment; however, only if hysteroscopic follow-up is provided in selected cases.[18,168]

10.4 Endometrial Protection During Hormone Replacement Therapy

Systemic and local progestogens are used to protect the endometrium from undergoing hyperplastic and neoplastic changes. Unless estrogen therapy is counteracted by progesterone, the endometrial proliferation is stimulated and the risk of endometrial carcinoma is increased 2- to 3-fold.[169]

Levonorgestrel administered into the uterine cavity has been shown to effectively oppose the estrogen-induced stimulation of the endometrial epithelium.[9,170,171] The levonorgestrel-releasing IUS consistently induces epithelial atrophy in the endometrium.[8,170,171] The endometrium of women receiving the oral progesterone treatment remained partly or mainly proliferative.[170] An additional advantage of adding the levonorgestrel-releasing IUS

to hormone replacement therapy is that most women have no menstrual bleeding after 1 year of therapy.[9,10,170] It is of utmost importance to investigate abnormal menstrual bleeding prior to inserting a levonorgestrel-releasing IUS and, if the bleeding pattern during the use of the IUS becomes abnormal, investigate the histology of the endometrium regardless of the patient's age.

10.5 Endometrial Protection During Tamoxifen Treatment

With the increasing incidence of breast cancer, tamoxifen is widely prescribed as a second-line treatment to prevent recurrence. As tamoxifen is partially an estrogen agonist, the risk of endometrial hyperplasias and even concurrent endometrial cancer are increased.[172] Three years of tamoxifen therapy leads to endometrial polyps in 29% of patients and to a glandulocystic atrophic appearance of the endometrium in two-thirds of patients.[172]

As the effect of levonorgestrel on the endometrial epithelium is strong and the plasma concentrations remain low, it seems logical to prevent the endometrial hyperplasia with intrauterine administration of levonorgestrel. In a study by Gardner et al.,[173] the levonorgestrel-releasing IUS prevented endometrial polyps from appearing and reappearing during the first 12 months of use. The long-term effects on the polyps remains to be seen.

11. Conclusions

The levonorgestrel-releasing IUS is a highly effective, fully reversible, long-term method of contraception. The effectiveness is comparable with all long-term methods including sterilisation. Furthermore, the use of the levonorgestrel-releasing IUS does not require operating room facilities and therefore does not expose the user to the risks relating to anaesthesia and operation. The return of fertility is rapid and the fertility rates are similar to other long-term methods of contraception and also to women without contraception. The health risks in association with the use of the levonorgestrel-releasing IUS appear to be minimal, while the health benefits are similar to those obtained with other methods of contraception, with the exception of sterilisation.

Continuance rates are high and user satisfaction can be increased with pre-insertion counselling, which should include discussion about efficacy, insertion procedure, lifespan, bleeding pattern, expulsion, perforation, pelvic infection and ectopic pregnancy. In addition, the levonorgestrel-releasing IUS radically alters the menstrual pattern and so the likely bleeding pattern with oligo- or amenorrhoea following 3–4 months of frequent light bleeding should be emphasised. The benefits of the levonorgestrel-releasing IUS make it a very suitable method of contraception for most women.

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