

Invited lecture to be held at the 5th Athens Congress on Women's Health and Disease, 26-29 Sept 2002 (to be published in the Annals of the New York Academy of Sciences).

Thursday, 26 September : 3.00-3.30 pm

Miniature Intrauterine Drug Delivery Systems

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INTRODUCTION

The search for effective, safe and convenient contraceptives has not diminished. Fifty years after the advent of the pill, there is still concern about its effect on haemostasis and the occurrence of breast cancer in some subgroups of women. The safety of sex steroids continues to be a major focus especially when used for contraception and for menopausal replacement therapy.

As oral contraceptives (OCs) are used by many women, 40 per cent of women of reproductive age and up to 70 percent in the younger age groups in certain western countries, it is important to give attention to their possible harmful effects. For several decades, and even today, epidemiological studies warn about the health risks associated with the estrogen contained in OCs, such as venous thromboembolism, and point to the need to develop hormonal methods that contain no estrogen.¹ In a small country like Holland, it is estimated that several hundreds of healthy oral contraceptive users are affected by sometimes life-threatening thromboembolic complications every year.^{2,3} Moreover, with regard to breast cancer, it is frightening to read that, also in Holland, oral contraceptives are responsible for several thousands of extra cases of breast cancer in former oral contraceptive users before the age of 70.⁴

These are the major potentially serious drawbacks of the method. In addition, women using oral contraceptive steroids are faced with nuisance side effects such as mood changes, weight gain, intermenstrual vaginal bleeding and spotting, loss of libido, to name a few. The latter has become a frequent complaint heard during family planning consultations.⁵ As these side effects very often lead to inconsistent use and discontinuation, many unplanned pregnancies occur. Trussell and co-workers calculated that the failure rate of OCs in the USA, after one year of use is about 5 per cent.⁶ This appears to be a worldwide phenomenon.⁷

At the other end of the life-cycle, women in the postmenopause are not free from adverse effects as a result of the use of postmenopausal hormone replacement therapy either. Only a few months ago the publication of the negative results of the Women's Health Initiative study (WHI)⁸, evaluating the safety of a particular brand of an estrogen-progestogen combination in postmenopausal women, elicited an unprecedented reaction in the press by women and doctors alike.⁹ "Women are mystified and confused", subtitles Time Magazine in its July 22 issue. Women were thought since the 80s that hormone replacement could serve as an all-purpose rejuvenator for women in the postmenopause.¹⁰ The overall health risk in the study, involving more than 16,000 women, exceeded benefits from the use of the conjugated equine estrogens 0.625 mg/day, plus MPA, 2.5 mg/day for an average of 5.2-years follow-up

among healthy postmenopausal women. The trial results indicate that there is an increased risk for coronary heart disease, stroke and venous thromboembolism, and increasing risk for breast cancer with increasing duration of treatment. Importantly, the part of the WHI study that evaluated the long-term benefits of estrogen alone did not show any adverse cardiovascular effect suggesting that the progestogen, MPA, might be to blame.

The least we ought to do is to inform women about their possible occurrence. Much better, however, is to focus on alternative administration routes to minimize adverse drug effects.

LONG-ACTING STEROIDAL CONTRACEPTIVE SYSTEMS

Over the years, many implantable, long-acting, steroidal delivery systems have been developed for contraception. The rationale is based on the knowledge that the occurrence of unwanted side effects and adverse reactions of steroid hormones are dose-dependent. It is, therefore, evident that the degree of risk diminishes in proportion to the dose. In medicine, it is a fundamental rule that medication should be used in the lowest possible dose sufficient to obtain effective treatment. This therapeutic concept of “minimal intervention” has been known for several decades but the practical applications have only recently become available.

Long-acting hormonal contraceptive systems can be classified as those designed for systemic and those for local delivery.¹¹ Among the non-biodegradable implantable and injectable systems, several have become available on the market (e.g. levonorgestrel, etonogestrel, DPMA, NET-EN). Progestogen/progesterone and combined intravaginal drug delivery systems for contraception and hormone replacement have been developed and are designed for systemic delivery. The hormones enter the bloodstream and, consequently, have a greater potential for dose-dependent side effects when compared to local delivery such as medicated intrauterine drug delivery systems where systemic absorption is minimal.

LOW-DOSE INTRAUTERINE STEROID-HORMONE DRUG DELIVERY

The approach followed by our group has been to develop long-acting methods which deliver the lowest possible dose to the endometrium to achieve minimal intervention fertility control without influencing normal ovarian function and/or causing hormonal adverse effects. In postmenopausal women, progestogens delivered directly to the uterine mucosa could avoid reversal of the beneficial effect of systemic estrogen replacement therapy.

Historical background¹²

Progestasert™ IUD

The first to have demonstrated the uterine effects of progesterone, in the late Sixties, was Dr. Antonio Scommegna (Michael Reese Hospital, Chicago). The initial objective of the development was to reduce the expulsion rate of IUDs by administering uterine relaxing hormones in the uterine cavity. This effect was not obtained as the expulsion rate did not differ from other IUDs. However, it was found that the intrauterine progesterone release significantly reduced menstrual blood loss. Dr. Scommegna postulated that the endometrial atrophy elicited by the natural steroid was the reason for the reduced menstrual bleeding and would also be useful to prevent implantation. He conceived a plastic T-shaped IUD, the vertical arm of which was replaced by a reservoir filled with crystalline progesterone (Figure 1). The Progestasert System marketed by the Alza Corporation in 1976 never gained wide popularity because of the short (one year) approved effective lifespan of the device. Moreover, the Progestasert probably gives inadequate protection against ectopic pregnancy

which is a serious drawback. A review on the Progestasert System was published by Soderstrom.¹³

Nova-T-LNG IUD (Mirena®)

Dr. Tapani Luukkainen, the inventor of the Nova-T IUD (a copper-T device with flexible arms) initiated his search for a long-acting steroid-medicated IUD in the early Seventies. The Nova-T-LNG emerged in 1976, a Nova-T IUD from which the copper filament had been removed and the vertical arm replaced by a small reservoir releasing a constant daily dose of 20 µg levonorgestrel (LNG) for at least five years (Figure 2). The commercial name of this device is Mirena (Leiras-Schering) and it is the first and so far only steroid containing IUD that is commercially available with an effective lifespan of five years. Its clinical effectiveness, resulting from atrophy of the endometrium and the physicochemical changes of the cervical mucus produced by the progestogen, is comparable with that of the combined OC when this is used correctly. Due to the low dose of LNG released, ovulation often is not affected. The main drawback of the Mirena device is that it produces amenorrhoea which may be a problem for some women particularly in southern Europe and in developing countries.¹⁴ However, the LNG-releasing intrauterine system has a much larger role than contraception. It is very useful for the treatment of menorrhagia and for endometrial suppression in postmenopausal women.¹⁵ Another drawback of the system is its size which is too big for use in the small uterine cavities of many postmenopausal and nulliparous women.¹⁶

With the 20 µg/day releasing Mirena IUD, lipid, lipoprotein and metabolic changes still may occur similar to the lipid changes seen with oral HRT (2 mg estradiol and 250 µg of LNG/day). The negative influence of LNG is dose dependent when administered with this intrauterine system. One study demonstrated a significant reduction in low density lipoprotein and a significant increase on high density lipoprotein in perimenopausal women treated with a 5 µg or 10 µg releasing Nova-T-LNG.¹⁷ This low dose of LNG did not reverse the beneficial effects on lipid metabolism seen after estradiol administration. It is therefore imperative to develop low-dose delivery systems that avoid any negative effect on lipid and lipoprotein profiles to maximize the cardiovascular protective effect of estrogen replacement therapy in peri- and postmenopausal women.

Hormonal side effects are also a problem in some Mirena users. These side effects occur, according to some studies, in up to 50 per cent of women and decrease with duration of use and age of the woman.^{18,19} Furthermore, Mirena may be associated with a higher expulsion rate when compared with copper bearing IUDs though this finding has not been consistent in all studies.²⁰ So, there is room for improvement.

THE "FRAMELESS" LNG IUS (FIBROPLANT-LNG)²¹

The frameless LNG intrauterine system (IUS) has been developed from the frameless GyneFix device²² and consists of two components (Figure 3): a 3 cm long coaxial fibrous delivery system, which delivers 14 µg/day of LNG for a minimum period of three years, and the conventional anchoring system used with the frameless GyneFix IUD. A version designed to last a minimum of five years is under development.

The fibrous delivery system is attached to the anchoring system by means of a stainless steel clip at the upper end of the fiber that is visible on ultrasound, to allow location of the system in the uterine cavity. The results of clinical studies conducted over the past five years with the frameless LNG-IUS suggest that the system is safe, well tolerated and effective as a contraceptive.²¹ Hormonal side effects have been almost absent due to the low systemic absorption of the drug. The frameless LNG-IUS is suitable both for contraception and the treatment of gynaecological conditions such as menorrhagia and dysmenorrhoea.²³ It can also

be used for endometrial suppression during estrogen replacement therapy. The two-component system is extremely simple and women-friendly, adapting to cavities of most sizes and shapes which is considered one of the main advantages of this new intrauterine LNG-delivery system.

The concept of anchoring the device in the myometrium is new and doctors need to be trained to become familiar with the technique of insertion which is now easier with the new upgraded Mark 2 inserter. In a multicentre clinical trial involving over 350 women, insertion failures have been minimal and no expulsion occurred.²⁴ In contrast with the 'conventional' IUDs, the anchored system is smaller, simpler in design and more flexible than the other IUD-frames that are available. The anchoring system also offers a greater efficacy, lower expulsion rate, higher tolerance and continuation rates.

T-SHAPED LNG-RELEASING IUDs

T-shaped IUDs have been used for several decades and health care providers are familiar with their insertion and fitting requires minimal training. The combination of drug delivery technology with a conventional IUD frame is, therefore, attractive for use by non-specialist providers (e.g. nurses, midwives, general practitioners) especially since the number of gynaecologists in Europe (e.g. Belgium, UK, the Netherlands, etc.) is likely to decrease in the future. Gynaecologists are also more and more subspecialized and the provision of contraceptives including IUD insertion are increasingly entrusted to general practitioners and nurses in, for example, United Kingdom, Scandinavia and the USA. The T-shaped IUDs are especially designed for this target group of health care providers whilst the anchoring technology can be used by doctors and nurses who have received special training. It has been demonstrated that appropriately trained nurses are competent at IUD insertion and their role in providing contraceptive care should be developed more widely.²⁵

T-LNG14 intrauterine device for parous women

The T-LNG intrauterine device was designed to maintain the advantageous effects of the 20 µg/day Mirena IUD whilst addressing reported difficulties in insertion and reducing troublesome side effects such as disturbed bleeding patterns, including amenorrhoea, and hormonal side effects.

The second reason for the development of the T-LNG14 IUD was to extend the lifespan of a progestogen delivery system to at least ten years.

The insertion procedure of T-LNG14 IUD is simple and straightforward. As the arms unfold immediately upon insertion of the IUD into the uterine cavity, the risk of perforation may be reduced (Figure 4).

T-LNG14 intrauterine device for nulliparous women

A major problem today is the increasing number of pregnancies in adolescent women. The problem is exacerbated since the majority of these pregnancies are unplanned and unintended.

These contraceptive failures are usually the consequence of lack of access to information and services, unwanted sexual relations, unprotected sex or ineffective use of contraception. In spite of the wide scale availability of OCs -at least in developed countries- and the significant progress in contraceptive technology which has been made in the past 40 years, there has been no reduction in unintended pregnancies in young women in the past decade. It seems extremely hard for young women to use contraception correctly and consistently. It follows that contraceptive method failure rates, for methods which depend on user compliance, may be calculated incorrectly and are probably reported lower than is the case.

Methods, which are dependent on memory and motivation, such as OCs, are not the ideal solution in the younger age groups. With injectables, implants and IUDs, the inherent efficacy is so high, and proper and consistent use is almost guaranteed, that studies invariably demonstrate extremely low pregnancy rates.^{26,27}

A major advantage of long-acting hormonal methods is that they eliminate the need for specific action at the time of coitus such as putting on a condom, or for daily administration. They offer discretion and privacy. Unfortunately, they also have disadvantages because they disrupt the menstrual cycle causing breakthrough bleeding, amenorrhoea or occasionally, heavier bleeding. They can also cause systemic hormonal side effects.

New developments in intrauterine technology are providing smaller frameless and framed intrauterine systems. Intrauterine devices and intrauterine drug delivery systems are particularly attractive as they have the advantage of acting locally, avoiding systemic effects. They have less impact on menstrual pattern after the first few months and, when low dose levonorgestrel intrauterine devices are used, they are less likely to cause initial spotting, amenorrhoea and hormonal side effects.

The small T-LNG14 with its small dimensions is such a system which can be easily inserted in the smaller uterine cavities of nulliparous women without local anaesthesia (Figures 5). Clinical studies suggest that the low dose released per day is sufficient to provide effective contraception although further studies are required to confirm the long-term efficacy.^{21,24}

This IUD is inserted in the same way as the T-LNG14 IUD for parous women.

T-LNG5 intrauterine device for post-menopausal women

The T-LNG5 IUD, releasing 5 µg/day of LNG was designed for several reasons: i) in order to reduce the cardiovascular risk in post-menopausal women of hormone replacement therapy (HRT), the use of a low-dose LNG-releasing systems for endometrial suppression using estrogen replacement therapy may be desirable and ii) to maximize ease of insertion, which is a problem with the Mirena IUD in postmenopausal women, and reduce the incidence of troublesome side effects such as hormonal side effects and effects on lipoprotein metabolism associated with conventional HRT. The T-LNG5 IUS has the same design as the T-LNG14 IUS for use in nulliparous women but a lower rate of daily release of LNG. The lower release rate of T-LNG5 could reduce side effects compared to Mirena in postmenopausal women. Specifically this includes the occurrence of hormonal side effects and a reduced or absent effect on lipid metabolism.^{17,28}

Experimental and clinical data indicate that progestogens can induce vasoconstriction of estrogenized vessels by down regulating the estrogen receptors in the arterial wall which could lead to increased vulnerability to vasoconstrictive events such as migraine and coronary arterial spasm. In addition, progestogens may also have direct progesterone receptor mediated-effects that oppose the actions of estrogen. Women receiving progestogens can experience chest pressure or chest pain or signs or symptoms of cerebral vasoconstriction. Angiographic and Doppler studies in these women have demonstrated coronary spasm, transitory ischemic attacks and increased cerebral pulsatility.²⁹ The vasoconstrictive effects of medroxyprogesterone acetate (MPA), the progestogen used in the WHI trial, have clearly been demonstrated in postmenopausal women using estrogens. Consequently, Sarrel proposed that the best method for delivering a progestogen to post-menopausal or climacteric women would be to deliver it locally to the endometrium, avoiding systemic effects.³⁰

CONCLUSION

Intrauterine contraception, in spite of the high level of effectiveness and acceptability has not been widely accepted. Ironically, of all effective birth control methods, intrauterine devices have the highest safety record but their use is low even if women are dissatisfied with taking OCs or any other method. The United States of America and the Netherlands are typical examples of very low use of IUDs.

User non-compliance is an ubiquitous phenomenon occurring particularly in young women but also in women using conventional menopausal treatment regimens.³¹ Even where motivation for daily use is good, compliance is often poor. This is not likely to change as the inadequacies of use are due to human error, lack of education and understanding. Furthermore, the occurrence of side effects and adverse reactions add to the problem.

Perhaps it is good to repeat what others said before: "We need to develop an attitude of zero-tolerance to thromboembolism". Hence, the need to develop long-acting steroidal drug delivery systems with minimal or no metabolic impact. As a result of technological progress, miniature, low-dose, long-term intrauterine drug delivery systems can offer women of all ages troublefree contraception and postmenopausal replacement therapy with enhanced effectiveness, reduced side effects and optimal user-compliance.

Despite the minimal absorption of the steroid in the systemic circulation, low-dose intruterine drug delivery systems deserve the status of a locally acting methods which should be regarded as fundamentally advantageous, if effective, to systemically applied medications which may have potentially inherent ill side effects.

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FIGURES

Figure 1. The Progestasert™ intrauterine device releasing 65 µg of progesterone/day for 1 year of use.

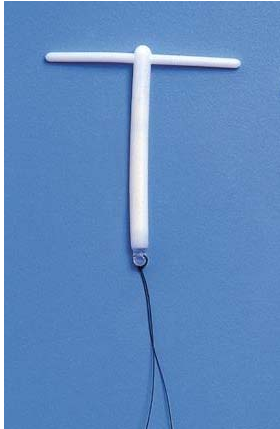


Figure 2. The Nova-T-LNG (Mirena®) intrauterine system releasing 20 µg of levonorgestrel/day for 5 years of use.



Figure 3. The FibroPlant-LNG intrauterine system releasing 14 µg of levonorgestrel/day (left). The FibroPlant-LNG intrauterine system in situ (right).

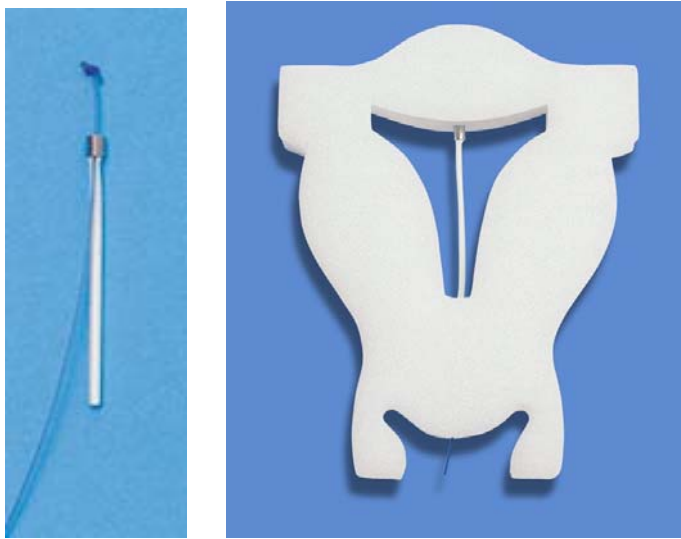


Figure 4. The T-LNG14 intrauterine device releasing 14 µg of levonorgestrel/day designed for for 5 to 10 years of use in parous women: insertion procedure.



Figure 5. The T-LNG14 intrauterine device releasing 14 µg of levonorgestrel/day for 5 years of use in nulliparous women (left). Section through the T-shaped LNG-releasing intrauterine device (right).

