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MINIATURE LONG-TERM INTRAUTERINE DRUG DELIVERY FOR MORE EFFECTIVE CONTRACEPTION IN ADOLESCENTS

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Abstract

New developments in the field of intrauterine drug delivery have the potential to challenge the oral contraceptive pill and revolutionize the use of intrauterine contraception in regions where current use of IUDs is extremely low and help reduce the unacceptable high number of unintended pregnancies and induced abortions in many countries in the world. Clinical trials and experience with the frameless mini GyneFix IUD for contraception in women with normal menstruations and the 'low-dose' frameless and framed LNG-IUS for use in women with excessive bleeding and/or dysmenorrhoea suggest that these developments could be very useful and increase the prevalence of use of IUDs significantly, including in nulligravid/nulliparous women.

Introduction

One of the great challenges of our time is to reduce the soaring number of unplanned pregnancies in adolescent women.¹ If the pregnancy is allowed to go to term (which does not happen in about 50 per cent of the cases)², there are several possible important medical consequences such as low-birth, prematurity, intrauterine growth retardation and neo-natal mortality.³ Adolescent pregnancy carries many other risks which has been the focus of intense research activity in recent years. Teenagers who become parents are at greater risk of social and economic disadvantage throughout their lives than those who delay childbearing until their twenties.⁴ They are less likely to complete their education, to be employed, and to be happily married; and they are more likely to have larger families and to receive welfare.⁵ More than 10 per cent of all births each year are to women between ages 15 and 19. The figures continue to rise in developed as well as developing countries.^{2,6}

A key issue: Contraceptive prevalence

"Contraceptive prevalence represents the key not only to improved reproductive health and environmental health, but also to demographic and economic development".

Egon Diczfalusy, *The Contraceptive Revolution*, 1996

In his remarkable article entitled: "Contraceptive prevalence, reproductive health and our common future", published in 1990, Diczfalusy wrote: *"The 1980s will go into history as a decade of lost opportunities to increase contraceptive prevalence and improve reproductive health worldwide. As the decade closes, 500 million couples still have no access to fertility regulation, there are 30-50 million induced abortions each year, 15 million infant and child deaths (30 per cent of all deaths worldwide), an estimated 250 million new cases of sexually transmitted diseases and 60-80 million infertile couples."*⁷ Over the last 10 years, the world has changed considerably. In many respects, the situation is far worse than 10 years ago. The UN estimated recently that population is growing by about 78 million per year. In certain regions of the world,

mainly sub-saharan Africa, fertility declines are lagging behind. Almost all population growth is in the developing world and about threequarters is urban. As cities grow ever larger, their impact on the environment grows exponentially.

Alarming increase in adolescent pregnancies — a world-wide problem

A major problem is the increasing number in pregnancies in adolescent women. Recent population studies have established the alarming increase of teenage pregnancies world-wide.^{9,10,11} We are facing the largest-ever generation of young people entering adulthood. Millions of women begin their childbearing in their teens, mostly out of marriage. The problem is huge since the majority of these pregnancies are unplanned and unintended. Some figures speak for themselves: more than 50 per cent of pregnancies in the USA are unplanned; half of them (1.4 million per year) end in termination of which over 50 per cent are in women younger than 25 years of age and 22 per cent in adolescents. In Western Europe, the figures are similar; in the UK, in France and Italy there are roughly 200,000 abortions yearly and 25 per cent of the women are between 16 and 19 years of age.

Teenage pregnancy is unquestionably a world-wide problem: 58 per cent of all mothers in sub-Saharan Africa are teenagers. A similar situation is seen in the Philippines, Thailand, India, Pakistan, Bangladesh and Central America.¹² In China, the number of unintended pregnancies and abortions in teenagers has sharply increased during recent years.^{13,14} As many as 4.4 million abortions may be sought by adolescent girls each year. A large numbers of these abortions are clandestine and therefore unsafe.

The majority of unintended pregnancies are usually the consequence of lack of access to information and services, unwanted sexual relations, unprotected sex or ineffective use of contraception. The latter can result from providing too few options, inadequate information or unsuitable methods for certain subgroups of teenage women. In spite of the widescale availability of the pill (at least in the Western world) 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 the past decade. The typical failure rate of the pill is still unacceptably high at 5 per cent due to inconsistent use and discontinuation.¹⁵ Between 40 and 60 per cent of new pill users discontinue the pill during the first year. The average duration of use of the pill in the USA is only 4.8 months. The same phenomenon has been observed in Western Europe where 50 per cent of adolescents stop using the pill after 3 months. It seems extremely hard for very young women to use the method correctly and consistently. It follows that contraceptive method failure rates, for methods which depend on user compliance, may be calculated incorrectly and be reported lower than reality.

Effective methods of contraception and optimal service delivery are needed

A shift to modern and effective methods is needed to ensure contraceptive security to women and couples who genuinely want to plan their family. In countries where contraceptive use is very low and fertility levels are very high, and have not started yet to decline, it seems urgent to assign to the delivery of effective family planning services the high priority it deserves.^{16,17}

LONGACTING SYSTEMIC AND INTRAUTERINE METHODS FOR USE BY ADOLESCENT WOMEN

Methods which are dependent on memory and motivation, such as the pill, are not the ideal solution in the younger age groups. The ineffectiveness of oral contraceptive pills and barrier methods of contraception was shown in studies conducted in young women in the UK who underwent a pregnancy termination.¹⁸ Most women used the condom method, which was followed by OCs. Both these methods were found to be ineffective because of user-dependent failures. The aim to prevent repeat unwanted pregnancy failed completely.

With oral contraceptives (OCs) there are also health-related concerns. 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. As 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 developed countries, it is important to give attention to their possible harmful effects. 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.¹⁹ In a small country like Holland, several hundreds of healthy oral contraceptive users are affected by sometimes life-threatening thromboembolic complications every year.^{20,21} 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 70.²² For years, 'the pill' has been synonymous with contraception. This has regrettably helped to maintain ignorance of any alternatives beyond condoms and sterilisation, although acceptable alternatives have demonstrated their superior effectiveness.

INJECTABLES AND IMPLANTS

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. In a comparative study in 100 postpartum adolescents of whom 50 selected the pill and 50 an implantable method (Norplant), one young mother in the Norplant group and 19 in the pill group became pregnant during the first postpartum year.²³ Similar results obtained in another study conducted in postpartum adolescent women.²⁴

It appears that the most effective method for young women is a method which minimises the risk of imperfect use.

Over the years, many implantable, long-acting, steroidal delivery systems have been developed for contraception. 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 action, such as the pill. They offer discretion and privacy. Unfortunately, some of them also have disadvantages because they disrupt the menstrual cycle causing breakthrough bleeding, amenorrhea or occasionally heavier bleeding. They can also cause systemic hormonal side effects and there is a higher incidence of weight gain. Furthermore, they can also cause a delay in return of fertility.

As the occurrence of unwanted side effects and adverse reactions of steroid hormones are dose-dependent, 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.²⁵

Long-acting hormonal contraceptive systems can be classified as those designed for systemic and those for local delivery. 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. Long-acting injectables, implants, IUDs and hormone-releasing intrauterine systems are methods which point the way forward, even if it takes time to learn how to insert them.²⁶

MINIATURE INTRAUTERINE SYSTEMS

Intrauterine devices and intrauterine systems are particularly attractive as they have the advantage of acting locally, avoiding systemic effects. New developments in intrauterine technology are providing smaller frameless devices and devices that combine the features of a frameless copper device with a levonorgestrel system or systems that release levonorgestrel only. The small copper-releasing devices have less impact on menstrual blood loss and, when low dose levonorgestrel intrauterine systems are used, they are less likely to cause amenorrhea and hormonal side-effects. They may be ideal for use in younger women because they are small, effective and well tolerated. Unlike the pill, they are genuinely 'fit-and-forget'. In use, they are much more effective than pills in this age group. Moreover they are longacting and reversible. So, the reward is substantial. The small copper IUDs are also very effective for emergency contraception.²⁷ However, copper intrauterine devices do not offer protection against sexually transmitted infections (STIs) and, therefore, they are not always the methods of first choice for teenagers. Such a protective effect has been observed with hormone-releasing intrauterine devices in women aged 25 and under although this finding was not confirmed in other studies.²⁸ Nevertheless, in the current situation, they should be offered more frequently as first or second line methods, in combination with condoms.

A recent re-assessment of the risk of pelvic inflammatory disease attributable to an intrauterine device suggested that the estimated risk was low, only 0.15, even in regions where the prevalence of STIs is high.²⁹ Furthermore, recent clinical evidence has shown that previous use of a copper IUD is not associated with an increased risk of tubal occlusion among nulligravid women.³⁰

Non-hormone-releasing IUDs

1. The Lippes Loop

Dr Jack Lippes, Buffalo, New York, developed the plastic Lippes Loop in the early 1960s with a research grant from the Population Council.³¹ He designed the double 'S' shape to accommodate the IUD to the triangular shape of the uterine cavity. At the same time, this design would make spontaneous expulsions less likely (Figure 1). The plastic material can be easily deformed and stretched, the intrinsic "memory" enabling the plastic to regain its original shape. When stretched, the 'double S' can be placed in an inserter tube thereby eliminating the need for dilatation of the cervix.

Because of its simple insertion and removal, acceptable rates of pregnancy and side effects were obtained. The Lippes Loop became the standard with which all IUDs were compared.

2. The TCu380A (Paragard)

Another major development, the TCu380A or Paragard, became available after a long 'incubation' period of about 15 years.³² Its design was based on anatomical studies conducted on human uteri, which revealed the T-shape of the contracted uterine cavity. Dr. Howard Tatum selected the T-shape plastic model because it seemed logical that this design could cause a minimum of distortion of the endometrial cavity during its maximum degree of contraction phase (Figure 1).

Dr. Tatum met with Dr. Jaime Zipper in Santiago de Chile, a professor in the department of physiology and the department of obstetrics and gynaecology at the University of Chile who had conducted studies on the contraceptive action of intrauterine copper.³³ Prototypes were developed with increasing copper loads. A high copper content, particularly when added to the crossarms of the T, is helpful in reducing the number of accidental pregnancies which occurred when the IUD moved downward into the isthmic region of the uterine cavity.

The Copper T 380A was approved by the US FDA in 1984 and quickly replaced the Lippes Loop as the standard IUD. Today, the TCu380A IUD remains the "gold" standard against which the effectiveness and safety of all IUDs are assessed.³⁴

Following the development of the TCu380A IUD, many new IUDs and systems for drug delivery were in development. However, there are only two developments which can truly claim superiority over the Copper T 380A IUD; these are the frameless copper IUDs and the levonorgestrel-releasing intrauterine systems.

3. The "frameless" GyneFix IUDs

3.1 GyneFix standard

The most common side effects of 'framed' IUDs are bleeding and pain. The prevalence of complaint of bleeding and pain vary according to both patient and the IUD used. In general, the greater the surface area and size of an IUD, the higher the incidence of removal for bleeding and pain. Young nulliparous women and those with low parity are particularly prone to report bleeding and pain. Disproportion between the IUD and the uterine cavity results from an IUD with a fixed shape and size that is inserted in a cavity that varies in shape and size in each woman. Even in the same woman, the uterine cavity changes slightly during the various phases of the menstrual cycle.

The frameless and anchored IUD was developed in 1985.^{35,36} Six copper tubes are fixed on a length of suture thread. The proximal end is provided with a knot which is implanted in the myometrium with an

inserter to permanently secure the IUD in the uterine cavity. With this new concept, dimensional problems are avoided.

GyneFix has a very low failure rate which is attributed to the optimal target delivery of the copper ions in the upper part of the uterine cavity. Its performance is further optimized by the atraumatic frameless design which minimizes the side effects and discomfort experienced with conventional IUDs. A summary of 15 years of clinical experience was submitted for publication recently.³⁶

3.2 GyneFix mini

A high copper-load is of minor importance with the frameless IUD since the device is attached to the fundus. Figure 1 shows a mini version of the GyneFix IUD (200 mm² total copper surface area) which is only 2 cm long (4 copper tubes instead of 6) compared with the Lippes Loop and TCu380A IUDs. Clinical trials with the '200-device' suggest a high efficacy similar to the higher load (330 mm²) standard version (Table 1).³⁷ Its small surface area, however, is 1/3 smaller than the regular GyneFix IUD, three times smaller than the TCu380 IUD and six times smaller than the Lippes Loop.

The magnitude of the increase in menstrual bleeding is related to the size of the device. With larger types of non-medicated IUD, i.e., Lippes Loop, the blood loss is about 70-80 ml, approximately double that of the normal menstrual flow (> 80 ml is defined as menorrhagia). The amount of excess bleeding is less (50-60 ml) with the smaller 'framed' copper devices. The majority of users of the GyneFix mini IUD have normal no or limited change in menstrual blood loss due to the small surface area.

Table 1. Events and gross cumulative discontinuation rates per 100 women at one year (interim analysis). Adapted from Wildemeersch et al. Contraception (accepted for publication) (with permission).

	All centres	
	No.	Rate \pm SD
Pregnancy	2*	0.98 \pm 0.71
Expulsion	3	1.04 \pm 0.60
Removal for bleeding and/or pain	1	0.39 \pm 0.39
Removal for 'other medical reasons'	4	1.49 \pm 0.75
Removal for 'other reasons'	0	
Removal for 'pregnancy wish'	3	1.51 \pm 0.87
Loss to follow-up	1	0.33 \pm 0.33
Continuation rate	286	95.02 per cent
Women recruited	301	
Women-months of use	4110.84	

* one pregnancy occurred following expulsion of the IUD

Hormone-releasing IUDs

Copper IUDs do not itself reduce bleeding. This can be achieved by delivering intrauterine progestins. Figure 2 shows three generations of progestin-releasing IUDs.

1. 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 2). 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.³⁸

2. T-LNG IUS (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.³⁹ Another drawback of the system is its size which is too big for use in the small uterine cavities of many nulliparous women.⁴⁰ Hormonal side effects are also a problem in some Mirena users. These side effects occur in a significant number of women and decrease with duration of use and age of the woman.^{41,42,43} 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.⁴⁴ So, there is room for improvement.

3. The "frameless" LNG IUS (FibroPlant-LNG)

The frameless LNG intrauterine system (IUS) has been developed from the frameless GyneFix device and consists of two components: 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 (Figure 2). 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.⁴⁵ The occurrence of hormonal side effects has been low due to the low systemic absorption of the drug. The frameless LNG-IUS is suitable for both contraception and the treatment of gynaecological conditions such as menorrhagia and dysmenorrhoea.⁴⁶ 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 disadvantage of the frameless intrauterine system is that the concept of anchoring a device in the uterine cavity is new. Doctors need to be trained to become familiar with the technique of insertion. However, improved insertion techniques are invented to speed up proficiency. In a multicentre clinical trial involving over 350 women, using a new insertion instrument, insertion failures have been minimal and no expulsion occurred.⁴⁷ It has been shown repeatedly in longterm clinical trials that, when properly inserted, expulsion rates of less than 1 per cent are the rule.³⁶ 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 offers a greater efficacy, higher tolerance and continuation rates.

4. The small T-shaped LNG-releasing intrauterine device for nulliparous women

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) and for doctors who are less experienced, or feel less comfortable with the anchoring technique. The T-shaped hormone-releasing IUDs are especially designed for this target group. Appropriately trained nurses can be taught to become competent IUD providers and their role should be developed more widely.⁴⁸

The small T-LNG IUD with its small dimensions is such a system which can be easily inserted in the smaller uterine cavities of nulliparous women without local anaesthesia. The vertical stem is loaded with LNG to provide a release of drug for a period of five years (Figure 3). The horizontal arms, which resemble the advantageous 'Cu-Safe' design, are highly flexible and unfold immediately upon insertion of the IUD into the uterine cavity, minimizing the risk of perforation. Clinical studies conducted with a low dose (14 µg) LNG-releasing IUD suggest that this low dose is sufficient to provide effective contraception although further studies are required to confirm the long-term efficacy.^{45,47}

Further comments and recommendations

Women consider contraceptive effectiveness the single most important property of a contraceptive method.⁴⁹ Long duration of action is also highly valued by women. For women who don't want to be pregnant again, the longer the method works, the better and most women would select a method that is reversible if they could choose. A "secret" method (from husbands and other family members) is important for women in certain developing countries but not in developed countries, although young women, especially adolescents, might wish to use contraceptives secretly. Women largely dislike methods that cause disturbance of the menstrual pattern. Amenorrhoe is strongly linked with the perception of ill-health although counselling may render amenorrhoea more acceptable.⁵⁰

Menstrual problems, including heavy bleeding and dysmenorrhoea, are common in adolescence, the first due to aberrations of hypothalamic control in the vast majority of cases, the second due to myometrial stimulation, in many cases secondary to the production of excessive amounts of prostaglandin.⁵¹ The intrauterine delivery of LNG is highly effective to treat both conditions.^{46,47,52} Contraception and treatment may, therefore, be a highly desirable combination. Figure 4 shows the menstrual bleeding scores (visual bleeding assessment according to Janssen et al.⁵³) before and during treatment with the FibroPlant-LNG system.

The challenge with intrauterine contraception is to apply new concepts to IUD design increasing the attractiveness of the method to women and their physicians. IUD designs suitable for emergency and post-abortion contraception are also welcome to prevent another unintended pregnancy and the repeat abortion this could result in.

Implantable methods are particularly needed for young women to reduce the number of unintended pregnancies and induced abortions. In the past the IUD was not recommended for use in young nulliparous women and those women with small uterine cavities. Traditionally, countries like France have been opposed to intrauterine contraception in nulliparous women.⁵⁴ However, new concepts and innovation in IUD design have enabled a drastic reduction in the size and volume of new generation IUDs making them more acceptable for this group of women and reduce the risk of expulsion.

WHO suggests that the benefits of IUDs generally outweigh the risks in women of any age, whether parous or not. In addition, the WHO approves the use of IUDs in women younger than 20, provided that these women are at low risk of sexually transmitted infections (STIs).⁵⁵ However, WHO advises against the use of IUDs in women who have had a positive PID diagnosis in the past 3 months.

Conclusion

New developments in the field of intrauterine drug delivery have the potential to challenge the oral contraceptive pill and revolutionize the use of intrauterine contraception in regions where current use of IUDs is extremely low and help reduce the unacceptable high number of unintended pregnancies and induced abortions in many countries in the world. Clinical trials and experience with the frameless mini GyneFix IUD for contraception in women with normal menstruations and the 'low-dose' frameless and framed LNG-IUS for use in women with excessive bleeding and/or dysmenorrhoea suggest that these developments could be very useful and increase the prevalence of use of IUDs significantly.

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FIGURES

Figure 1. Three generations of copper IUDs: Lippes Loop (1960), TCu380A (1980), GyneFix mini (2000).



Figure 2. Three generations of progestin-releasing IUDs: Progestasert IUD (left) and T-LNG IUS (Mirena) (middle) and frameless FibroPlant-LNG intrauterine systems (right) inserted in a foam uterus.

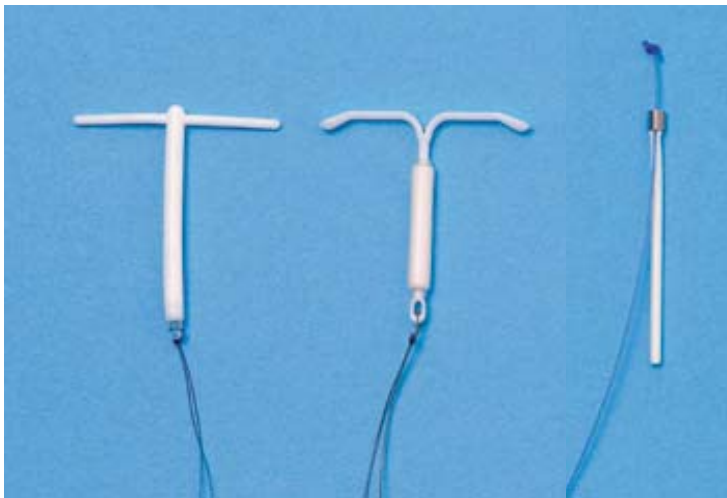


Figure 3. The T-LNG14 intrauterine device releasing 14 µg of levonorgestrel/day for 5 years of use in nulliparous women (left). Section through the T-shaped LNG-releasing intrauterine device (right). The entire stem of the device consists for the matrix drug delivery compartment.

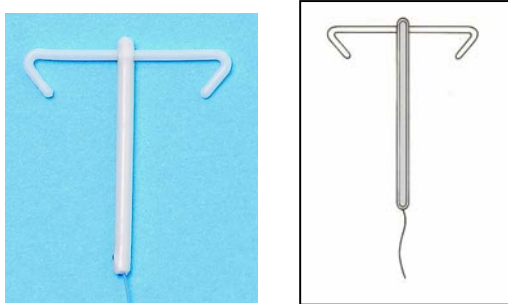


Figure 4. Reduction in menstrual blood loss with FibroPlant-LNG. Mean visual bleeding scores and standard deviation in women before and during treatment (p = 0.002).

