

GynePlant: preliminary clinical experience with a copper and levonorgestrel releasing intrauterine system

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Abstract

A novel intrauterine contraceptive drug delivery system derived from the conventional frameless (GyneFix) intrauterine implant system (IUS) is described and the results in 30 women are discussed. The first objective of the development of the GynePlant-levonorgestrel (LNG) system is to reduce menstrual bleeding by combining a shortened version of the standard GyneFix implant, having a copper surface area of 200 mm², with a system for the sustained intrauterine delivery of levonorgestrel. The system releases 5 µg of LNG per day. The results of a pilot study using a LNG delivery system releasing 14 µg of LNG per day suggest that the GynePlant system, apart from being well tolerated, is safe and effective. The LNG-component appears to have a beneficial effect on the amount of bleeding. The results of the current study suggest that the GynePlant IUS, releasing 5 µg of LNG per day is effective in preventing pregnancy and to reduce or stabilize menstrual bleeding.

Introduction

The low pregnancy rate with the GyneFix IUS is attributed to the high delivery of copper ions to the upper part of the uterine cavity. As a consequence, the pregnancy rate with GyneFix is lower than with those of the most effective high-load copper devices currently used. Rates are also seen to be lower than those of the TCu380A (Ortho Gyne T380) intrauterine device (IUD)^{1,2}. Other studies have shown that young parous and nulligravid/nulliparous women using GyneFix are no more susceptible to pregnancy than other age groups; the annual pregnancy rate is close to zero (0.1% per year). No ectopic pregnancies were diagnosed in any studies with GyneFix. A review of 15 years of clinical experience with the frameless IUS is available.³

Geometric compatibility between the IUD and the uterine cavity is the key to the success of and IUD. Due to its design characteristics, GyneFix has a low removal rate for pain, both among parous and nulligravid women. The flexible GyneFix adapts perfectly to the curvature of the uterine axis, so reducing the likelihood of endometrial/myometrial trauma.

Although the removal rate for bleeding is low, abnormal bleeding still occurs with GyneFix in a number of women as a result of the copper effect on the endometrium. Copper ions are known to disturb the homeostasis of the endometrium. Heavy menstrual periods sometimes occur, especially during the first few months after insertion. These heavy periods may frighten some uninformed women and lead to removal of the implant.

One could conclude that abnormal bleeding is the main drawback of the frameless copper releasing IUS. To overcome this problem, the following approach was evaluated: 1) by reducing the amount of copper and 2) by combining copper with a steroid releasing system delivering a small quantity of hormone directly on the endometrium continuously for years. Levonorgestrel has shown to be very effective in reducing menstrual blood loss.⁴

A previous study with the GynePlant IUS releasing 14 µg of LNG per day was published earlier.⁵

The present study was conducted to obtain further clinical experience with a combined copper and levonorgestrel-releasing implant system which releases a lower amount of levonorgestrel.

Material and method

GynePlant differs from the conventional GyneFix implant system in that it consists of a non-biodegradable suture thread made of surgical monofilament polypropylene onto which four (instead of six) copper tubes are threaded, providing a total surface area of 200 mm². The upper and lower tubes are secured onto the thread to keep them in place and the top of the thread has a knot which serves as an anchor. Attached to the lower copper tube extends a fiber of 1.2 mm in diameter and four cm in length delivering approximately 5 µg of levonorgestrel per day (Figures 1 and 2). The total length of the copper element and the fibrous delivery system is 3 cm. The anchoring knot is implanted into the myometrium of the uterine fundus with a specially designed insertion instrument, so permanently securing the device in the uterine cavity.

Between August 2000 and December 2001, 30 GynePlant were inserted in women at low risk for sexual transmitted infections (STIs). All insertions were performed by the first author. Fifteen nulliparous and fifteen parous women received the device for routine contraceptive use. Women's subjective assessment of the amount of blood loss, with or without the presence of clots, was used to characterize the blood loss. A sexual history was taken but no systematic screening for STIs was carried out. All insertions in the nulliparous group were accomplished under intracervical anaesthetic using a dental syringe. One cartridge of 3% mepivacaine was injected at 3 and 9 o'clock in the compact tissue of the cervix at the level of the internal os using the transcervical technique; and at 5, 6 and 7 o'clock in the posterior lip of the cervix, approximately 1 cm deep.

Oral informed consent was obtained and the study was approved by the local ethical committee of the University of Ghent, Belgium.

After insertion, the women were requested neither to have intercourse, nor to use tampons for the first 3-5 days. No additional contraceptives were prescribed but the advice was given to use a condom in case of risk behaviour.

Follow-up visits were scheduled at 1, 3, 6 and 12 months after insertion, and yearly thereafter. Besides, patient were asked to come to the clinic any time problems occurred.

Since the number of insertions is small, no statistical analysis was performed. The events will be evaluated on an individual basis.

Results

By the end of December 2001, 20 of the recruited women had the system in place for at least 12 months. There was one expulsion and one removal because of low insertion in a severely retroverted uterus. There were no pregnancies or PID cases recorded (Table 1). The GynePlant device was well tolerated. The majority of women reported slight spotting mainly during the first weeks following insertion of the implant. In general the menstrual periods were less in amount or the same as before, as judged by the women themselves.

Table 1. GynePlant: number of terminations in 30 users.

<i>Reason for termination</i>	<i>Number of removals</i>
Pregnancy	0
Expulsion	1
Bleeding	0
Pain	0
PID	0
Other medical reasons	1

Discussion

It is very important to widen the choice and acceptability of contraceptive methods. Apparently, the options are very limited as evidenced by the outbreak of adolescent pregnancies worldwide, the high prevalence of induced abortions and the increasing reliance on sterilization, which is carried out at younger and younger ages.⁶ In some countries of sub-saharan Africa over 50% of all mothers are less than 20 years of age. In India and Pakistan this figure is on average 16% and also in the Philippines, Thailand, Bangladesh and in Central America, the magnitude of unwanted teenage pregnancy is huge.⁷ It is difficult to assess the acceptability of contraceptives but the high discontinuation rates of the existing methods and discomfoting side effects are indicative that there is still a need for improving the acceptability of contraceptive methods. Women are largely dismayed at the prospect of a contraceptive method that causes abnormal menstrual bleeding or amenorrhoea. Bleeding disturbances account for most of the removals of IUDs.⁸ Most IUD users want to have a bleeding pattern which is not too much different from what they were used to before the insertion of the device.

The levonorgestrel-releasing intrauterine system (Mirena[®]), releasing 20 µg of levonorgestrel per 24 hours has shown to reduce menstrual blood loss considerably, but also causes amenorrhoea in up to 20 percent.⁹ Nevertheless, the reduced bleeding is definitely beneficial. However, the levonorgestrel-releasing IUD also has unwanted hormone-related side effects in some women such as mood changes, headache, nausea, acne, functional ovarian cysts, prolonged light bleeding and spotting and amenorrhoea which may be due to a too high release rate of levonorgestrel. The lower release rate of 5 µg with the GynePlant system may therefore be more appropriate and cause less side effects.

The effectiveness of a method is the single most important factor valued by women. The reduced surface area of copper (200 mm²) of the GynePlant device does not seem to affect the effectiveness of the device. Since the amount of copper released may be directly related to the amount of blood loss, a reduction of the release rate may cause less disturbance of the

homeostasis of the endometrium. This is what was experienced in a recent study conducted with the GyneFix-200 IUS.¹⁰

The development of the frameless device is a response to the growing need to develop high-performing, long-acting, reversible and acceptable contraceptives with a high continuation of use. Its performance is further optimized by the atraumatic frameless design which minimizes the side effects and discomforts experienced with conventional IUDs. The GynePlant is a further development which may offer additional advantages particularly with respect to reduced bleeding.

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Figures:

Figure 1. GynePlant in uterus



Figure 2. Cumulative LNG-release curve (X = T(days), Y = Release (mg))

