

REVIEW ARTICLE

GyneFIX®. The frameless intrauterine contraceptive implant - an update for interval, emergency and postabortal contraception

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"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

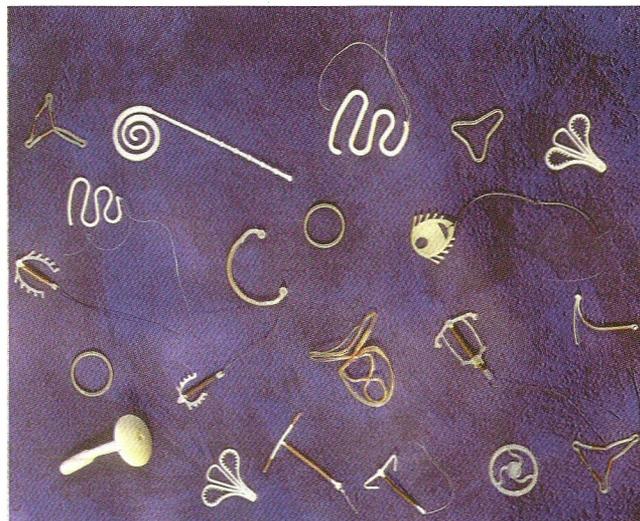
Summary

This article reviews the clinical experience with the GyneFix intrauterine implant system for interval, emergency and post-abortion contraception. The relatively high rate of unintended pregnancies and abortions in the world signifies that greater access to contraception is necessary. Unwanted pregnancies and abortions could be avoided by widening the range of effective and acceptable contraceptive methods for use in situations where current methods are far from optimal. High effectiveness, protection against sexual transmitted infections, long duration of action, reversibility and safety are some of the most important attributes of contraceptives valued by women.

The development of the frameless intrauterine device is a response to the need to develop contraceptives with high

user continuation rate. GyneFix has the lowest failure rate of all copper IUDs currently available. Its performance is further optimised by the atraumatic frameless design which minimises the side effects and discomfort experienced with conventional IUDs. GyneFix could, therefore, be a useful new contraceptive option in looking at ways to reduce the number of unwanted pregnancies and induced abortions.

Figure 1 A collection of old and newer 'framed' IUDs taken from the museum of Professor M Thiery



*Originally, the clinical testing of GyneFix® was started by a group of gynaecologists working at the University of Ghent, Belgium, under the name IUD-group led by Professor M. Thiery, which later became the International Study Group on Intrauterine Drug Delivery. Experienced in intrauterine contraception over more than 25 years, the group's members studied intrauterine devices in collaboration with organisations, drug companies and individual researchers. The group continues to study innovative drug delivery technologies, aimed at finding improved methods for prevention and treatment of gynaecological conditions, improvements to birth control methods, and higher levels of safety, user acceptability, compliance and quality of life for women.

Introduction

The first intrauterine contraceptive device (IUD) promoted specifically for contraception was described in 1909.¹ Since then, numerous IUDs have been developed and marketed (Figure 1). As the IUDs have been perfected, the method has become one of the most effective contraceptive options yet developed. Currently, the copper-containing devices are the most effective and most widely used IUDs in the world.²⁻⁶

IUD use provides effective protection against pregnancy. When compared with women who use other reversible methods of contraception, those who use IUDs have the lowest mortality attributable to those methods and to the consequences of unwanted pregnancy and childbirth.⁷⁻⁹

The major improvement in IUD development over the past 35 years has been in pregnancy rate or efficacy. The most significant drawback with the use of IUDs has been the patient continuation rate, although the continuation rate for IUDs generally is better than for oral contraceptives. The two major contributors to a low continuation rate are spontaneous expulsion and patient-requested removal for bleeding and/or pain (Table 1).^{6,8,10}

Table 1 IUD discontinuation rates (after 1 year of use)⁸

Reason	Per 100 women
Pregnancy	05-5.0
Expulsion	5-15
Removal for bleeding/pain	5-15

Over the years, many researchers have come forward with new technologies to reduce the incidence of menstrual or intermenstrual bleeding problems, to minimise complaints of pain and consequently to improve convenience of use and continuation rates. However, improvements in these rates with the newer copper IUDs have been modest and little reduction in the rates of discontinuation for medical reasons have been obtained. With steroid-releasing IUDs, the amount of menstrual bleeding is significantly reduced, but at the expense of an increased incidence of spotting and amenorrhoea and other side effects.¹¹

There is a widespread unmet need for effective and acceptable family planning methods in many parts of the developing world and it has been stressed over the years that new strategies should be worked out which address this need.¹² In many developing countries, rapid population growth makes it difficult for food production to keep up with demand.¹³ The high number of unwanted births and induced abortions, the high discontinuation rate of existing reversible methods and the increasing reliance on sterilization carried out at earlier ages confirm this unmet need.

In addition, there is a need for more effective, reversible and acceptable contraceptives to reduce the high number of unwanted pregnancies and abortions in developed and developing countries.

The challenge of intrauterine contraceptive researchers, therefore, is to develop the ideal contraceptive device which has the attributes listed in Table 2.

Table 2 Ideal attributes of intrauterine contraceptives

- Prevent pregnancy effectively,
- Be well tolerated,
- Not become displaced or expelled,
- Be long-lasting,
- Have a strictly local effect,
- Not cause menstrual disturbances,
- Prevent sexually transmitted infection (STI),
- Be easy to insert and remove,
- Be relatively cheap,
- Be usable as an emergency contraceptive

In order to obtain optimal results, even the best intrauterine contraceptive device needs skillful insertion. Proper training in IUD insertion has sometimes been forgotten in the past. One of the consequences of lack of proper training is the greater chance of incorrect insertion with subsequent increase in problems leading to a poor image of the IUD and underuse of the method.

Another aspect of IUD insertion which needs careful attention is selection and careful counselling prior to and appropriate advice following insertion. It is important to inform every woman about all available methods and help her to choose a method. Counselling should also include an explanation of the mechanism of action.² IUDs are often underused because they are misunderstood and misconceptions about intrauterine contraception are still widespread.¹⁴ Many people believe that women cannot use an IUD until they have been pregnant. It may surprise many that the IUD is as safe or safer than other forms of contraception (even in nulliparous women).⁹

This article describes the background, rationale and clinical results of a new concept for delivering bioactive substances in the uterus, the GyneFix implant system. Ten years of clinical development have preceded the regulatory approval and marketing of GyneFix in the European Union. Today, an increasing number of women rely on the method to fulfil their contraceptive needs.

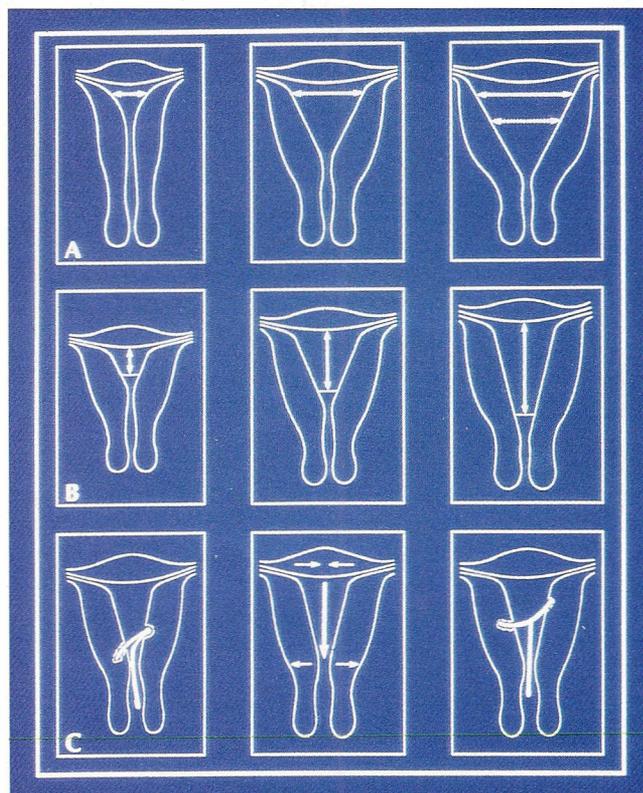
Background and technical development of GyneFix®

Rationale for the development. 'Individual variations in the size and shape of the human uterus are probably greater than variations of the human foot' (H M Hasson). This comparison, although devoid of any 'eloquence', is very appropriate. Both Dr Hasson from Chicago and his German counterpart, Dr K H Kurz, developed instruments in the early 1980s to measure the uterine cavity and to study the relationship between the IUD and the endometrial cavity related to side effects and complications. Both came to the conclusion that the performance of an IUD is to a large extent dependent on the presence or the absence of disharmony between the IUD and the uterine cavity in which it is placed. Method failure, expulsion, side effects such as bleeding and pain could be associated with geometric factors (Figure 2).¹⁵⁻¹⁷ The following is an analysis based on cavimetric findings.

The *contraceptive effect* of medicated intrauterine devices is closely related to the amount of active agent within the uterine cavity.^{19,20} Conception is, therefore more likely if the contraceptive substance is reduced as a result of downward displacement of the device or low insertion of the IUD in the uterine cavity. Optimal contraceptive efficacy is obtained when the IUD is located in the fundal part of the uterine cavity.

It is evident that *total expulsion* of the IUD offers no protection against pregnancy. However, also *partial expulsion or displacement* of the IUD in the isthmic or cervical region of the uterus often results in failure of the method.^{15,16} Incompatibility between the uterine foreign body and the endometrial cavity causes myometrial distension and/or irritation of the trigger zones of the uterus resulting in displacement of the device or its partial or total expulsion. Depending on the degree of the disharmony, translocation of the IUD often results in severe *cramping pain and abnormal bleeding* although the latter may have other causes. Examples of severe disharmony are given in Figure 2. In addition, it has been tentatively proposed that *intrauterine infection* may be promoted by injury caused by mechanical factors associated with a non-fitting or partially

Figure 2 Individual variation in width (a) and length (b) of the uterine cavity and (c) functional changes of the uterine cavity and examples of incompatibility (C1 and C3)¹⁵⁻¹⁶



A. Individual variation in width of cavities
B. Individual variation in length of cavities
C. Functional changes of the uterine cavity and examples of incompatibility (C₁ & C₂)

embedded IUD. It is possible, though unproven, that any trauma associated with the arms or stem of the IUD on the wall of the uterus encourages proliferation of any pathogens present.²¹

In 1984 a new direction, breaking entirely with current IUD technology, was taken by the design of anchoring systems for the suspension of tubular copper within the uterine cavity. Whereas all other IUDs possess either a solid plastic frame loaded with copper wire and/or sleeves (TCu380A), GyneFix is different. It is flexible, frameless and fixed into the fundal myometrium.

With this new concept, a plastic frame to retain the IUD became superfluous, thus overcoming dimensional problems. Consequently, the generation of expulsive forces, responsible for many of the undesired side effects and the expulsion problem related to the use of previous IUD models, is avoided.

Product characteristics

GyneFix[®] implant system. The GyneFix consists of six copper sleeves, each 5 mm long and approximately 2.2 mm in diameter, threaded on a length of suture material. The upper and lower sleeves are crimped onto the suture thread to prevent the sleeves from sliding off. The total surface area of copper, including the inner and outer surfaces, is 330 mm². The proximal end of the thread is provided with a knot which is placed in the fundal myometrium with an inserter, at a controlled depth of 1.0 cm, and acts as an anchoring system (Figure 3). Notably, the GyneFix lacks a plastic frame and this accounts for its flexibility. The anchoring system is essential for retention of the frameless device.

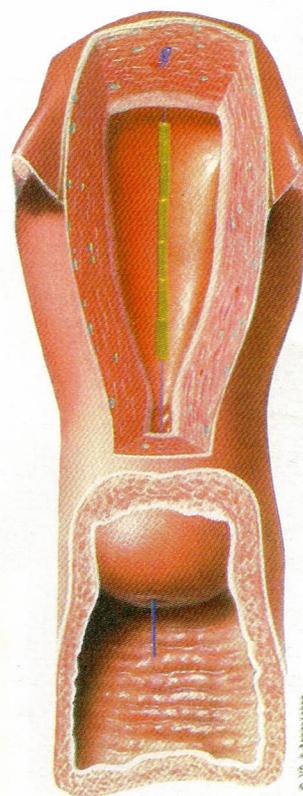
GyneFix[®] insertion system. The insertion instrument to anchor the GyneFix implant system in the fundal wall of the uterus consists of two parts. The 3.8 mm wide tube is semi-rigid and carries a movable flange (Figure 4). The plunger has a stainless steel stylet which is moulded into the plastic rod; its pointed end is specially shaped with a 'shoulder' or notch which carries the anchoring knot (Figure 5). The proximal end of the plunger is a handle. The different components of the insertion system are illustrated in Figure 6.

Practical clinical training in GyneFix[®] interval and GyneFix[®] post-abortion insertion

Proper GyneFix insertion reduces the risks of pregnancy and of all major side effects commonly seen with conventional IUDs.

History taking and screening. Prior to GyneFix insertion a woman needs to have discussed all her contraceptive

Figure 3 GyneFix[®] implant system.



options and be allowed to choose the method of her choice. As GyneFix insertion involves instrumentation of the cervix with its attendant risk of transmission of cervical infection it is essential to assess, by careful history taking and, if necessary, testing, the woman's risk of sexual transmitted infections (STIs). During the discussion about GyneFix, she needs to understand its effectiveness, duration, mode of action, effect on the menstrual cycle, method of insertion (with or without local anaesthesia), and the need for regular thread checks.

Important aspects of proper insertion of the GyneFix[®]

An informed woman. If the woman wishes, the use of local (intracervical) anaesthesia using a dental syringe (Figures 7 and 8) or PCB (paracervical block) anaesthesia should be

Figure 4 Peel-pack containing loaded GyneFix® inserter and uterine sound.

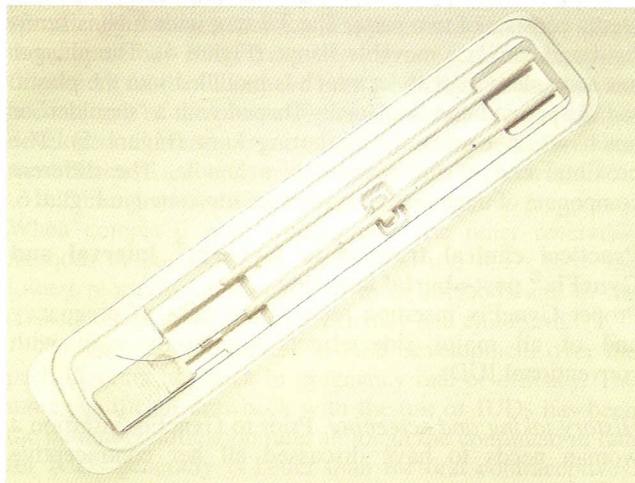
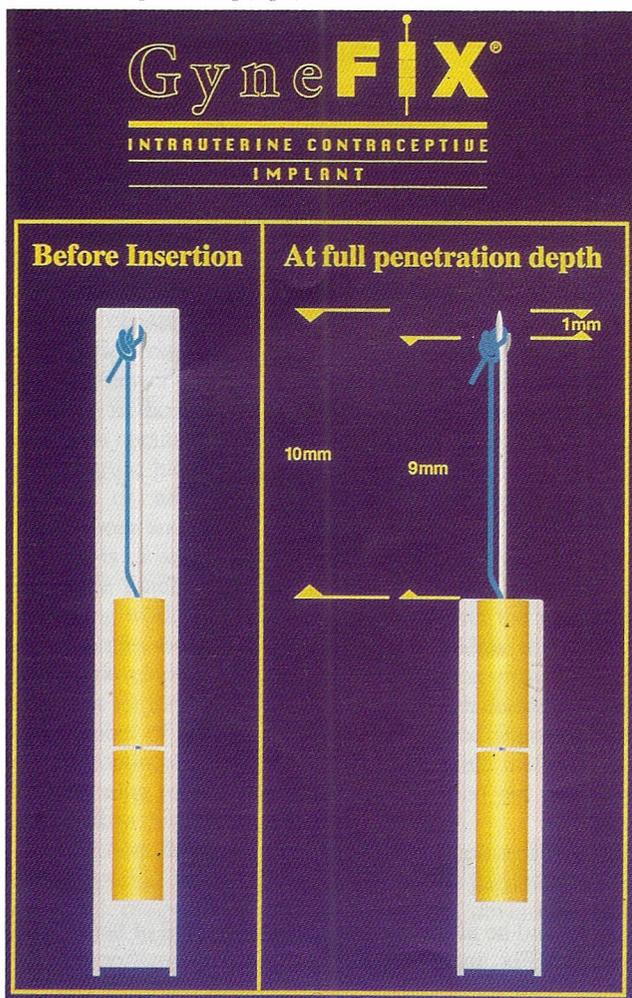


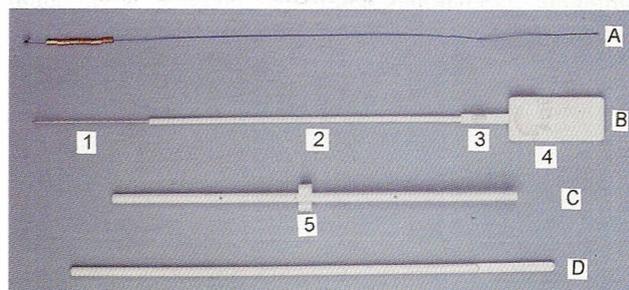
Figure 5 Illustration of the tip of the loaded inserter prior to anchoring (left) and during anchoring (right).



considered. Explaining the procedure and responding to her questions and concerns increases confidence and reduces anxiety. This helps the woman relax. The use of local anaesthetics appears to cause fewer vasovagal attacks, less pain at and after insertion and a lower removal rate for pain and bleeding in the first year.¹⁸

The proper technique: controlled insertion. Inexperienced doctors may have some fear of perforation during insertion of their first GyneFix-devices simply because of its anchoring technique. At the same time, proper anchoring is the single

Figure 6 GyneFix implant and insertion system. A= The GyneFix implant; B=the plunger (1=stainless steel stylet; 2=plastic rod; 3=middle segment; 4=handle); C=3.8 mm wide tube provided with cm marks, flange (5); D=4.0 mm wide uterine sound.



most important prerequisite for the optimal performance of the implant. Here are the key recommendations:

- *Always conduct a pelvic examination* to know the position of the uterus.
- *Guarantee alignment* of the cervical canal and uterine cavity as the inserter is not very flexible. The tenaculum or atraumatic forceps (preferably 18 to 20 cm long Allis Figure 9 or similar forceps) should not be placed too high on the cervix to allow proper traction to straighten the uterine axis, especially in case of marked retroversion or anteversion.
- *Always sound the uterus* to know the direction and depth of the cavity and to gain confidence that insertion is possible.
- *Don't proceed with the insertion if sounding is impossible* or if you have any doubt whatsoever.
- *Insert the GyneFix applicator up to the fundus* like the sound and keep it in contact with the fundus until the thread is released.
- *Concentrate in placing the anchoring knot* slowly and gently in the fundus of the uterus. The placement of the anchor is by a single manoeuvre, performed with such control that you are confident that the implantation is to the correct depth even if the inserter tube did not provide a mechanism to stop the stylet at the correct point.
- *Check with an ultrasound scan* if you have any doubt and remove the implant if it is not in the correct position.

Timing of insertion. GyneFix IN (interval version) can be inserted at any time during the menstrual cycle. It is evident, however, that the provider should rule out the presence of an implanted pregnancy if insertion of the device is planned in the second half of the menstrual cycle. The GyneFix PT (postabortal/post-termination version) should be used for insertion immediately after spontaneous or induced first trimester abortion of preferably less than 10 weeks gestation.

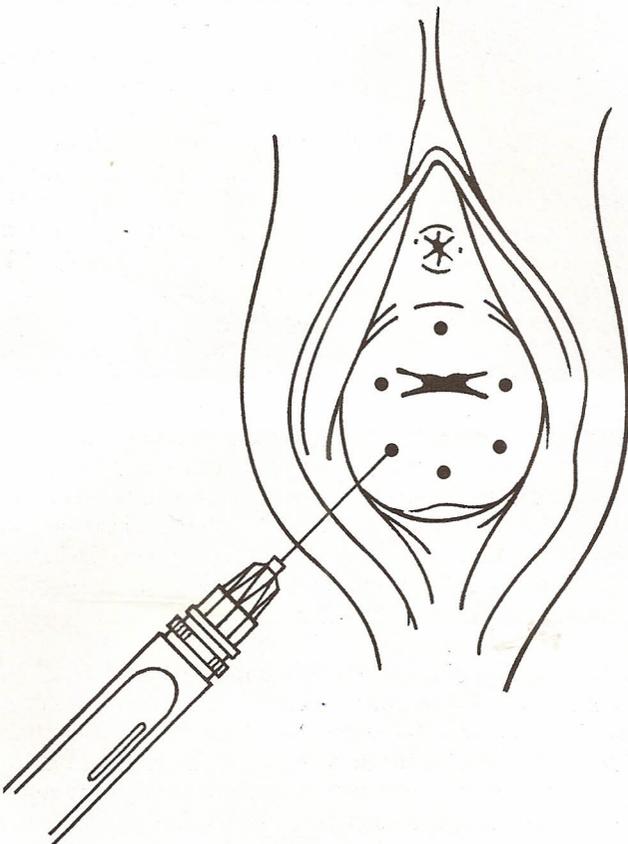
In non breastfeeding women GyneFix has been fitted from six weeks post partum. Although the IN version has been used, it is preferable to use the PT version initially as this is retained better (the PT version has a slightly bigger knot). Once the woman has had a spontaneous menstrual period the IN version can be used with confidence as the uterus will have involuted completely by then. In breast feeding women the IN version has been fitted successfully from twelve weeks post partum.

Ultrasound evaluation. Ultrasound examination is an effective means of evaluating whether the GyneFix implant has been properly inserted. For those who are starting GyneFix insertions, an ultrasound check is recommended to build up confidence in the technique. In a long-term study of 405 women, who used GyneFix for five years, it was

Figure 7 Dental syringe with 30G short needle.

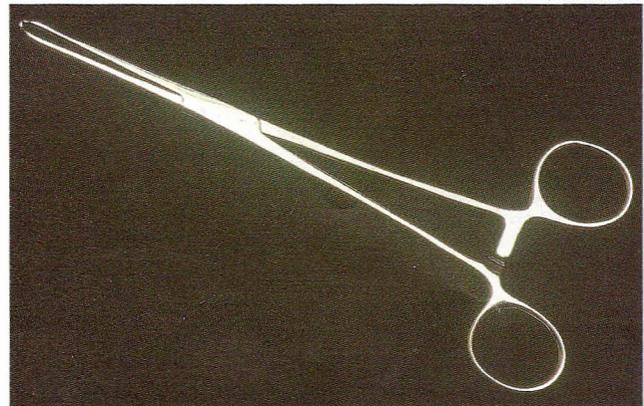


Figure 8 Intracervical anaesthesia for IUD insertion (author's technique). The injection of one cartridge (1.8 ml) of 3 per cent mepivacaine at 3 and 9 o'clock in the hard tissue surrounding the internal os, and at 5, 6 and 7 o'clock, one cm deep, is usually enough to provide pain relief. An additional injection can be given in the anterior lip of the cervix prior to the placement of the tenaculum.



shown that the average distance between the peritoneal surface of the uterus and the first copper sleeve (S-S distance) is 12.7 mm. The minimum was 10 mm and the maximum 28 mm in a myomatous uterus.²² Another important finding from this study was the absence of migration of the anchor, confirming the efficacy and reliability of the anchoring system (Figures 10 and 11). On rare occasions, an S-S distance at insertion of 9 mm has been measured and the implant was found to be in perfect position at follow-up. It is recommended to remove the implant if an S-S distance of less than 9 mm is found on ultrasound examination at the time of the insertion. The only exception might be if the woman has no complaints and the insertion was not accompanied by a sharp pain which is clearly in excess of that which is normal and unavoidable: this may be indicative of puncture of the serosa. Similarly, if the S-S distance is significantly greater than 20 mm, in the presence of a normal uterus, then the implant should be removed unless it appears to be well fixed on exerting gentle traction on the thread.

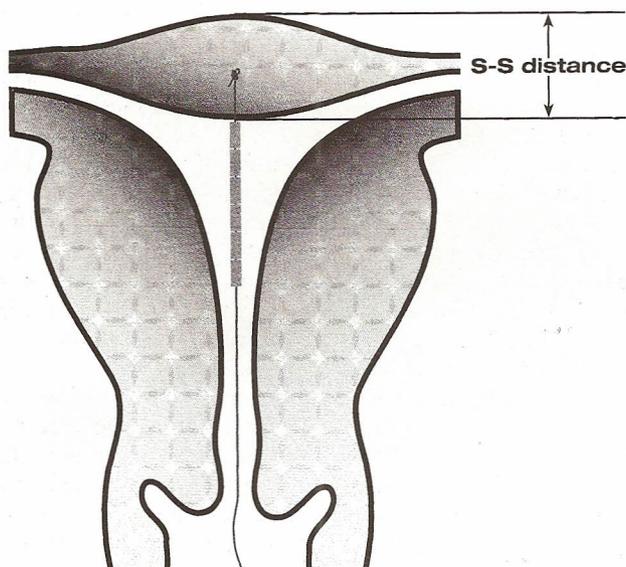
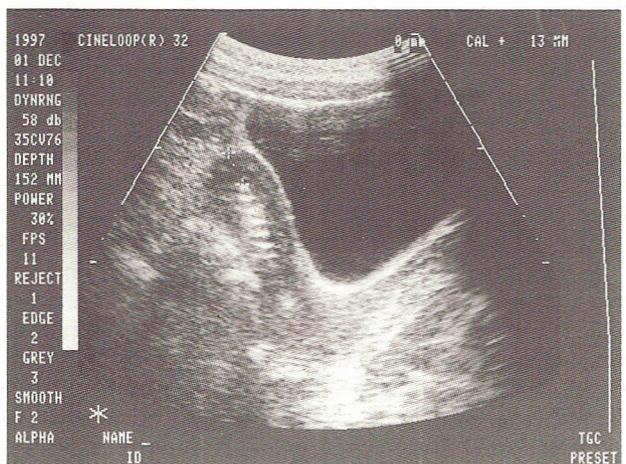
Figure 9 Eighteen cm long Allis forceps.



Safety of the anchoring system. The myometrial tissue reaction at the site of the polypropylene anchor was studied using a scoring system devised by Sewell.^{23,24} The interval between the insertion and hysterectomy varied from one day to four years. In one third of the specimens there was total lack of tissue reaction in the myometrium, whereas in the remaining two-thirds the reaction was slight to moderate (Figures 12 and 13). The diameter of the inflammatory response in the two uteri showing marked reaction did, however, not exceed one millimeter. In two other specimens, removed four years after insertion, no tissue reaction was found. No transplanted endometrial tissue could be observed within the adjacent myometrium in any of the cases studied.²⁴ This study supports both the safety of the material and the safety of the implant system.

Removal and reinsertion. GyneFix can remain in place up to five years or longer if recommended by the physician (eg women over 40). GyneFix can be removed from the uterine cavity by exerting traction on the thread. The removal force is on average three to four times the force to remove a T-shaped device.²⁵ This is not a difficult or traumatic procedure. If it cannot be seen, it may have retracted in the uterus, or the implant may have been expelled. Presence of the implant can be assessed by X-ray or ultrasound examination. If the thread has retracted into the uterine cavity, a forceps or a special thread retriever can be used to retrieve the thread from the cavity or removal can be accomplished by hysteroscopy.

Figure 10 and Figure 11 Measuring the S-S distance (surface of the uterus to first copper sleeve) by ultrasound, though not an imperative examination, is recommended to become familiar and to gain confidence in the insertion technique.



GyneFix can be replaced immediately after removal. If it is suspected that the device is not in the correct position at the time of insertion or thereafter, it should be removed and a new device should be inserted.

Advice after insertion. Advice to the user after insertion of GyneFix should include :

- Information on common side effects the user may notice after insertion: slight bleeding for a few days and heavier periods in the first few months after insertion. In case of spotting or heavy bleeding (after exclusion of infection and other local causes), the use of one of the following medications may be useful: estrogens/progestogens, NSAIDs, anti-fibrinolytic agents.
- Information on the possibility of early expulsion and on how to check for presence of the thread.
- Information on the warning signs of potentially serious complications (signs and symptoms in women and men which should lead to suspicion of infection).

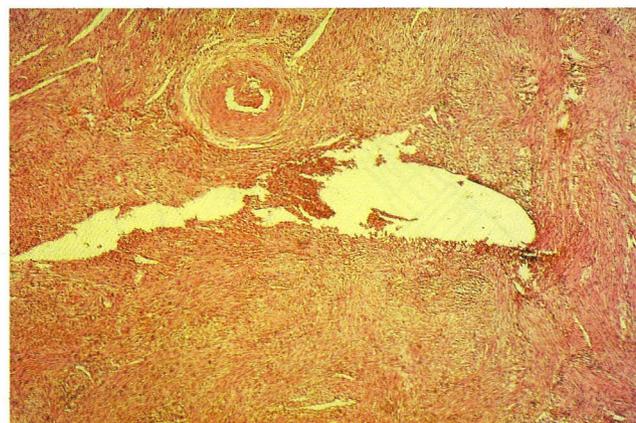
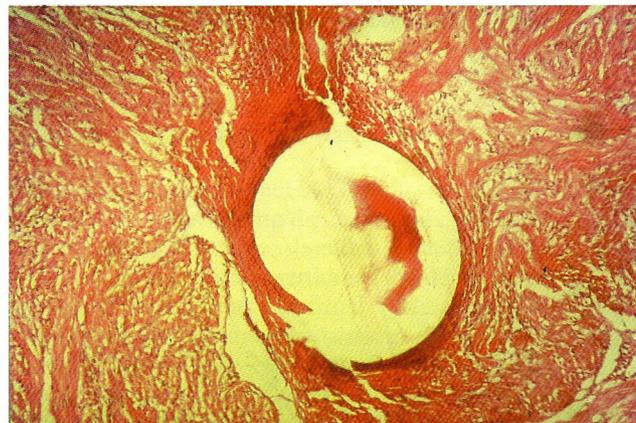
Following GyneFix insertion the doctor may arrange a follow-up visit after about one month mainly to check if the device is still in place or sooner if the insertion took place after an abortion. The purpose of the visit is also to reassure the woman about any common side effects and address any

other concerns or questions and to remind her, if appropriate, of the means to avoid STIs and the warning signs of pelvic infection.

Important points to tell the GyneFix® user

- She should **not use tampons for the first three to five days** after insertion and she should **inspect her pads during the first menstruation** to ensure that GyneFix has not been expelled.
- She can have sex as usual (no sex for three to five days after insertion of the GyneFix). If the thread bothers her partner, it can be cut short at the clinic, although the thread often softens after a while.
- Although pregnancy and PID have been rarely observed, she should see a doctor immediately at the first signs of pregnancy (period late, abnormal spotting or bleeding) or of pelvic infection (abdominal pain, dyspareunia, offensive discharge, fever).
- **Menstrual bleeding** may be heavier and last longer. There may be spotting, especially in the beginning. This usually settles down.
- She should know that she has a GyneFix implant and **when it needs to be replaced**.
- **If she gets pregnant, the GyneFix should be removed** as soon as possible if the thread is visible or palpable.
- She should know that **GyneFix offers no protection against STIs** and if she does not have a long-term, mutually monogamous sexual relationship, she should use additional protection, such as condoms.
- **Follow up** should be arranged according to local practice.

Figure 12 and Figure 13 Cross section through anchor site showing absence of tissue reaction (top) and minimal foreign body reaction (bottom).



Use effectiveness studies with GyneFix®

Effectiveness of GyneFix®. GyneFix is a very effective contraceptive device. Long term clinical studies are consistent and have shown very low pregnancy rates. Additionally, the pregnancy rate with GyneFix is lower than those of the most effective high load copper devices currently used (Figure 14). After the first year, a long term randomized comparative clinical trial has shown the pregnancy rate to be lower than that of the TCu380A IUD (Figure 15).^{26,27} The higher rate in the first year can be explained by deficiencies in the insertion procedure (see Footnote to the Figure) which have been remedied since and much lower rates are now obtained. Greater efficacy is of added importance because of the potentially increased morbidity when a woman becomes pregnant with an IUD in situ.⁹ Other studies involving over 1000 women have shown that young parous and nulliparous/nulligravid women using GyneFix are no more susceptible to

pregnancy than other age groups: the annual pregnancy rates are close to zero (0.0-0.1).²⁸ It is remarkable that no ectopic pregnancies were diagnosed in women fitted with GyneFix in any of the studies. This is reassuring since the prevalence of ectopic pregnancy in Western societies is approximately one ectopic for every 100 pregnancies.²⁹

The low pregnancy rate with the GyneFix is attributed to the high delivery of copper ions to the fundal part of the uterine cavity. Ultrasonographic studies conducted in women fitted with conventional IUDs have shown that the further the distance of the IUD from the uterine fundus, the greater the risk of pregnancy.^{19,20}

Expulsion of GyneFix®

Interval/post-menstrual insertion of GyneFix . The initial studies with the implant technology, followed by ultrasonographic and histologic evaluation of the anchor site and assessment of the traction force required for retrieval of the GyneFix demonstrate that the anchoring principle is a valid concept.³⁰⁻³² These studies also show that the anchor does not migrate over long periods of time.²² With conventional IUDs young and nulligravid/nulliparous women are particularly prone to downward migration and expulsion of the IUD. This, however, is not the case with the GyneFix. Long-term multicenter clinical trials using the current improved GyneFix insertion instrument showed very low expulsion rates both in parous and nulliparous which range from 0.1 to 2.2 per cent in large-scale multicentre open and randomized comparative clinical trials,^{31,32} as compared with expulsion rates between 2.7 and 17.0 per cent with conventional IUDs, during the first year of use (Figure 16). High partial and total expulsion rates are observed particularly in nulliparous women using conventional IUDs.³³⁻³⁵

The initially somewhat higher expulsion rates observed in the beginning of clinical trials or when a particular centre starts using GyneFix is due to lack of familiarity with the new anchoring technique. Most expulsions occur within a few months after insertion. A properly inserted GyneFix implant is rarely expelled and cumulative expulsion rates at five years of less than 1.0 per cent have been reported.²⁸

Figure 14 Gross cumulative pregnancy rates per 100 GyneFix users at three years as compared with the gross cumulative pregnancy rates per 100 TCu380A, MLCu375 and TCu220 users (non-randomised comparative studies conducted by the International Study Group on Intrauterine Drug Delivery)^{28,57}

Cumulative pregnancy rate at 3 years

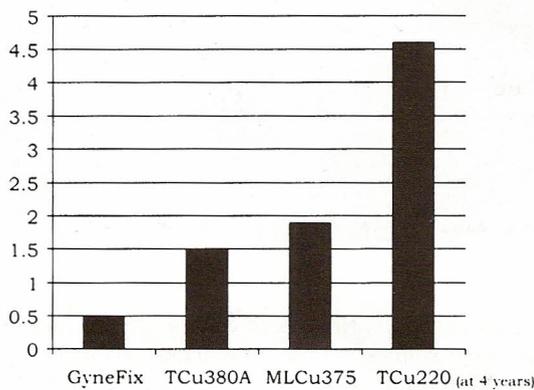
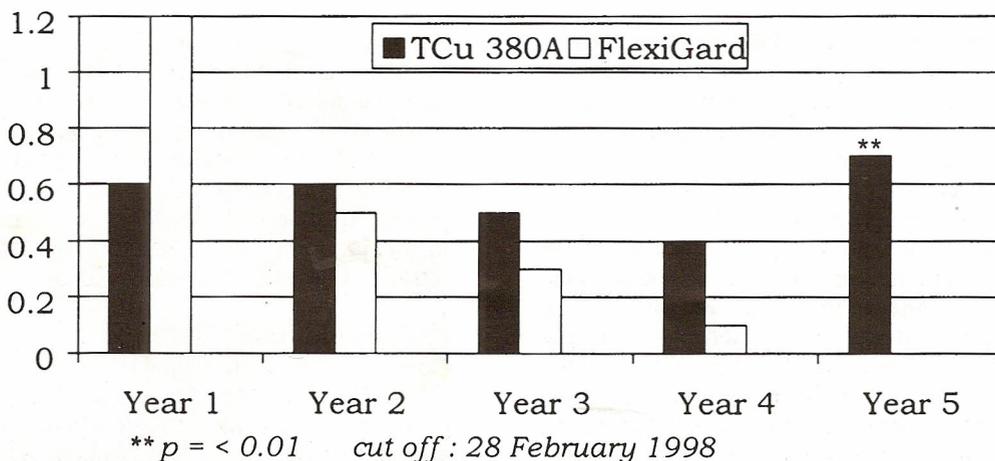


Figure 15 Randomized comparative trial TCu380A vs. The Frameless IUD (FlexiGard prototype implant system) in 2,000 women each. The first-year higher pregnancy rate with the frameless device is caused by the high failed insertion rate due to shortcoming of the insertion apparatus and implant (the majority of the accidental pregnancies occurred in the absence of the implant in the uterine cavity).^{26,27}

**Annual Total Pregnancy Rates per 100 Women
TCu 380A vs. the Frameless IUD (FlexiGard)**



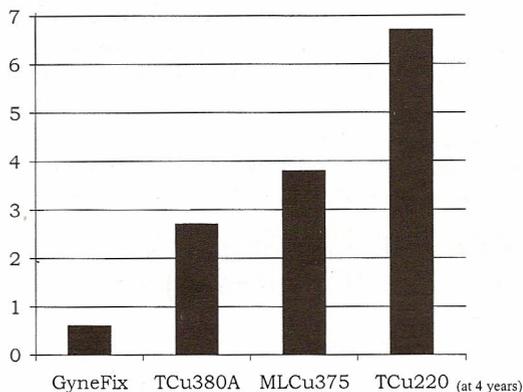
The reliability of the implantation technology is indirectly shown by the traction force needed to remove the anchor from its position in the uterine wall: on average amounting to 6.0 Newton (unpublished data), which is significantly higher than that needed for the removal of a standard T-shaped IUD (1.0-1.7 Newton), and comparable to the removal force of the MLCu-model (5.4-5.8 Newton). However, this does not mean that one has to pull hard to remove the implant.²⁵

Post-abortion insertion of GyneFix. The good retention of the GyneFix implant prompted the developers of the GyneFix to initiate studies of the insertion of specific versions for use immediately after induced or spontaneous abortion.

An international clinical study was initiated in 1995 to evaluate the expulsion rate when the device was inserted in a post-abortion uterus of less than 10 weeks gestation. The study is still ongoing. Although the number of insertions is small (N=125), there were no expulsions and no pregnancies in women followed up for at least one year (+/- 1300 women-months of experience) showing that the post-abortion version of the GyneFix is as well retained in the post-abortion uterus as when inserted post-menstrually. It was also reported that insertion of the device is easy and safe.³⁶ This initial positive experience with post-abortion insertion of Gynefix is currently being repeated in centers in the UK,³⁷ Belgium and other countries with similar results of high performance and absence of complications.

Figure 16 Gross cumulative expulsion rates per 100 GyneFix users at 3 years as compared with the gross cumulative expulsion rates per 100 TCu380A, MLCu375 and TCu220 users (non-randomized comparative studies conducted by the International Study Group on Intrauterine Drug Delivery).^{28,57}

Cumulative expulsion rate at 3 years



Bleeding/pain with GyneFix®. Due to its design characteristics, flexibility, near absence of a frame and the reduced space it occupies in the uterine cavity, GyneFix has a low removal rate for bleeding and pain. Nulligravid and parous cavities tolerate the GyneFix device.²⁸ Figure 17 shows an X-ray picture of GyneFix adapting to the curvature of the uterine axis thus reducing the likelihood of endometrium/myometrial trauma. Figure 18 shows 3-year data from studies with different intrauterine devices. In the GyneFix study, one quarter of users were nulliparous. The design characteristics of the device and the fact that hormonal menstrual problems are less frequent in younger women explains the very low removal for bleeding/pain in this group of women.³⁸ More data from studies conducted in nulligravid and nulliparous studies are being collected

Figure 17 X-ray of GyneFix in situ showing adaptation of the implant to the curvature of the uterus.



which appear to confirm these results. In two randomized comparative studies, on the other hand, conducted only in parous women the difference in removal rate for bleeding between GyneFix and the TCu380A IUD was not statistically different although a preliminary menstrual blood loss study showed less bleeding with the frameless device when compared with the TCu380A IUD.³⁹ Additionally, in this same study no decrease in ferritin levels were found with GyneFix after one year of use.

Although abnormal bleeding still occurs with the frameless device, and some women need medication such as NSAIDs or antifibrinolytic drugs, abnormal bleeding and/or spotting seems less of a problem if not associated with pain. Clear and detailed counselling prior to insertion improve acceptance of the device. Annual removal rates for bleeding/pain lower than 1.0 per cent have been reported for GyneFix in short-term and long-term non-randomized and randomized comparative studies.^{28,32}

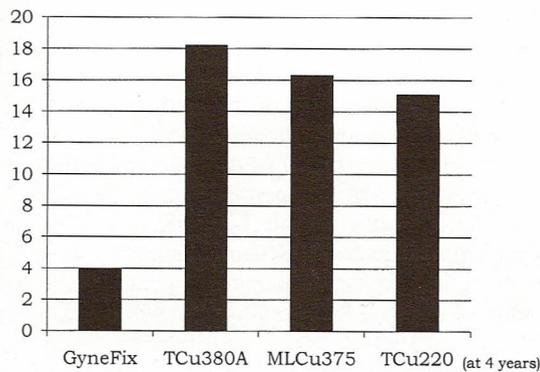
Notably, the majority of parous and nulliparous GyneFix users, with the exception of the initial period following insertion, do not report significant changes in their bleeding pattern. If abnormal bleeding occurs, it usually is not a major problem and acceptable by most (face-to-face interviews taken from hundreds of GyneFix users).

Complications with GyneFix®

Complications with GyneFix (eg Pelvic inflammatory disease, ectopic pregnancy and perforation) have been rare during the entire clinical trials conducted in more than 5000 women covering over 12 000 woman-years of experience.

Figure 18 Gross removal rates for medical reasons per 100 GyneFix users at 3 years as compared with the gross cumulative removal rates per 100 TCu380A, MLCu375 and TCu220 users (non-randomized comparative studies conducted by the International Study Group on Intrauterine Drug Delivery).^{28,57}

Cumulative medical removal rate at 3 years



Ectopic pregnancy. More than one per cent of pregnancies in North America and Northern Europe are ectopic.²⁹ GyneFix, like other copper IUDs with large amounts of copper (TCu380, ML375) offers significant protection against ectopic pregnancy. There have been no reports of ectopic pregnancies with GyneFix in any of the clinical studies conducted. In randomised comparative clinical trials, a few ectopic pregnancies have been observed with TCu380A but the differences were not statistically significant.^{26,32} Women who have had an ectopic pregnancy in the past do not necessarily have to be refused the use of the GyneFix since the device will reduce the risk between 10 and hundredfold.

Sexual transmitted infection (STI). Pelvic inflammatory disease (PID) has very rarely been observed in GyneFix users in large scale open and randomised comparative studies.^{26,28} There appears to be a greater risk with 'framed' IUDs as shown by these studies but the differences are not significant. The absence of a plastic frame, and the fact that the frameless device is completely contained in the inserter tube at the time of insertion, may be the reason for the reduced PID rate observed in randomized comparative clinical trials.

Data from a long term WHO study indicate that the risk of PID in IUD users is higher only during the first three weeks following insertion of an IUD and that the risk does not increase with long-term use.⁴⁰ The reason for the increased risk of infection after IUD insertion is that bacteria in the vagina/cervix can be transported into the uterine cavity during insertion. All potential users should, therefore, be screened by taking a proper sexual history and asked about signs and symptoms of these infections. Ideally, except in situations of known low STI prevalence, screening for Chlamydia trachomatis should be done. Practising aseptic insertion techniques, and conducting a follow up examination at one month are additional safeguards to prevent infectious complications in IUD users.⁴¹

Several reviews, studies and round table discussions have addressed the relationship between IUDs use and the occurrence of PID. They were reviewed by Beerthuizen.⁴² The findings indicate that PID risk is minimal in women who are at low risk for STIs, in other words, among couples in monogamous sexual relationships. Age and parity by itself is not a contraindication for the use of an IUD.

Women, who are at higher risk because of their sexual behaviour and other life style factors, have a higher risk of developing PID and should be discouraged from using an IUD. Doctors should also help their clients understand how they can protect themselves by using a back-up method (eg condom) in all new relationships.

Perforation. The occurrence of perforation with conventional IUDs in large studies is 1.3/1000 insertions.⁶ Perforation at insertion or delayed perforation or migration has not been recorded in large international multicenter clinical trials with the frameless device.^{26,28,32}

A small number of insertion related perforations have, however, been reported after market introduction of GyneFix in Europe, which may be attributed to inexperience with the technique of insertion, to improper technique or to a pathological condition. At least one perforation has been caused by softening of the uterine fundus due to degeneration of a fundal myoma which could not be detected prior to insertion of the device. The implants were removed by laparoscopy or (mini)laparotomy and no longterm consequences have been reported.

It should be emphasized that perforation can be minimized by carefully following the instructions for use (see key recommendations in Section 2).

Experience with GyneFix® in the UK

The avoidance of unwanted pregnancies and abortions is still one of the great challenges of our time. In the UK there were 177 000 abortions in 1996. The rates are highest among women aged 16 to 19 (25 per cent) and those aged 20 to 24 (27.2 per cent).⁴³ To quote the late David Bromham: 'Reduction of abortion will not be achieved by criminalization, legal limitation of access or financial limitations of access. Reduction of abortion numbers and rates requires more openness regarding sex and sexuality, including good education programmes and greater access to more effective methods of contraception'.⁴⁴ The experience with GyneFix indicates that GyneFix offers a new option that could increase contraceptive choice and therefore may help in reducing abortion rates.

Widespread training was initiated in the UK in the Spring of 1997 after formation of a Steering Group of experts in family planning from all over Britain. Information on the product was given to the potential users and providers with guidance provided in a Training Manual prepared by the International Study Group on Intrauterine Drug Delivery and with inputs from the Steering Group and the UK Family Planning Association.

Interval insertion of GyneFix®. The first UK centre to introduce the GyneFix was Abacus in Liverpool. An audit of the first 210 insertions, more than half of them in nulliparous women and a quarter for postcoital use was carried out. This showed that inspite of some discomfort at insertion, acceptors were very satisfied with its performance. No pregnancies were observed and removal rates for side effects were low. Expulsions have occurred, some of which may be related to operator inexperience. GyneFix is felt to be a welcome addition to the contraceptive menu especially for the nulliparous.^{45,46}

Post-abortion insertion of GyneFix®. Immediate post-abortion insertion of GyneFix was started in the autumn of 1997 at St James's University Hospital, Leeds. Thirty one insertions of GyneFix PT were performed immediately following suction termination of pregnancy. Thirty of 31 insertions of GyneFix PT were successful. The median gestational age (range) was

10 (8-13) weeks, and median uterine length (range) was 10 (8-13) cm. The initial experience suggests that GyneFix is suitable for immediate post-abortion insertion with less risk of expulsion when compared with traditional IUDs. GyneFix offers continuous contraception to prevent repeat abortions. These data confirm the data obtained in other studies.³⁶

Use of GyneFix® as an emergency contraceptive

GyneFix is a useful option for emergency contraception because, like other conventional IUDs, it can be inserted up to five days after unprotected intercourse to prevent pregnancy and provide ongoing contraception. Copper IUDs work by preventing fertilization and implantation of a zygote and are, therefore, not abortifacient agents.^{47,48} Most women requesting emergency contraception are young and nulliparous. As GyneFix can be a first choice contraceptive in nulliparous women, it is very suitable for them for continuous use if they are at low risk for STIs. IUDs are more effective in preventing unwanted pregnancy than post-coital pills (pregnancy rate <0.1 per cent).⁴⁹ The Yuzpe regimen is effective in preventing three out of four pregnancies, but must be started within 72 hours of intercourse.^{47-49,58} Recent studies conducted by the World Health Organization indicate that levonorgestrel-only pills are more efficient.⁵⁹ Experience in the UK has shown the significant potential of GyneFix for emergency contraception.⁴⁶

GyneFix® as an alternative to female sterilisation

According to research, around 50 per cent of couples above the age of 40 in the UK rely on sterilisation of one or other partner to prevent pregnancy. The main drawback of sterilisation is that it is difficult to reverse and it involves surgery. Figures state that up to 10 per cent of sterilised women request a reversal operation, the results of which are not predictable. Before referring a woman for sterilization, all other options including an IUD should be offered especially in younger women.⁵⁰ If GyneFix is used, it is probably not necessary to replace the device in women who had it inserted after the age of 40 years since the risk of failure is negligible at this age.

GyneFix® in nulliparous women

In the past, it has been said that women over 25 years or older are the best candidates for IUD use, and women over 35 the ideal candidates. This misconception stems from studies conducted in the 70s and early 80s which showed that pelvic inflammatory disease is more frequent in nulliparous users compared to women using other methods of contraception.⁵¹ This recommendation, based on the fear of PID and the potential for resulting infertility, is no longer justified.

In young nulliparous women, IUDs are usually a second-choice though very acceptable one if they are properly counselled and proper screening is performed prior to insertion. GyneFix offers the nulliparous women choices which until now have been restricted mainly to parous women: to use a longlasting, effective, easily reversible non hormonal contraceptive.⁵²

Unintended pregnancy in young women. A high proportion of young women using oral contraceptives discontinue further use because of perceived hormonal side effects and menstrual problems. Others do not use the method correctly.⁵³ Methods which avoid noncompliance have been shown to be much more effective than the pill in preventing pregnancy in young women.⁵⁴

When considered for use by nulliparous women, conventional IUDs should be used with caution because of

the higher risk of expulsion and dysmenorrhoea. Dimensional incompatibility is more likely to occur in nulliparous women. Additionally, traumatic lesions to the endometrium and myometrium are expected to be more frequent in nulliparous women due to disharmony.^{55,56} Researchers have also suggested that these lesions may enhance the risk of infection.²¹

Randomised comparative studies between GyneFix and conventional IUDs have not been conducted in nulligravid/nulliparous women. The usefulness of these studies could be questioned since a lower performance and a significantly higher rate of side effects with 'framed' IUDs are likely as a consequence of dimensional problems. Moreover, randomized comparative studies with T-shaped devices in parous and nulliparous women have concluded that the failure rates of the T-shaped device (including TCu380A) in nulliparous women are significantly higher when compared to those in parous women.^{33,34} Similar high rates of removal for bleeding/pain and for expulsion of the device are observed in nulliparous women. The ultrasound pictures in Figures 19 and 20 show the marked difference in size between the nulligravid uterus (Figure 19) and parous uterus (Figure 20). The frameless device fits equally well in both uteri. It follows that, when selecting an IUD for nulliparous women, the effect of incompatibility between the IUD and the uterine cavity should be taken into consideration.

Conclusion

The discomforts of earlier models of IUD are no longer acceptable. 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. GyneFix has the lowest failure rate of all copper IUDs currently available. Its performance is further optimized by the atraumatic frameless design which minimizes the side effects and discomforts experienced with conventional IUDs. GyneFix could, therefore, be very helpful to reduce the number of unintended pregnancies and induced abortions.

It is the responsibility of health care providers and the media to put all methods, including intrauterine ones, into the right perspective and provide information about their beneficial characteristics and advantages as well as any drawbacks to enable women to make fully informed choices which should lead to greater satisfaction and therefore lower rates of discontinuation and failure.

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Figure 19 and Figure 20 Ultrasound illustration of the frameless implant system in a small nulliparous uterus (top) and a much larger parous uterus (bottom) demonstrating compatibility in these two very different uteri.



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