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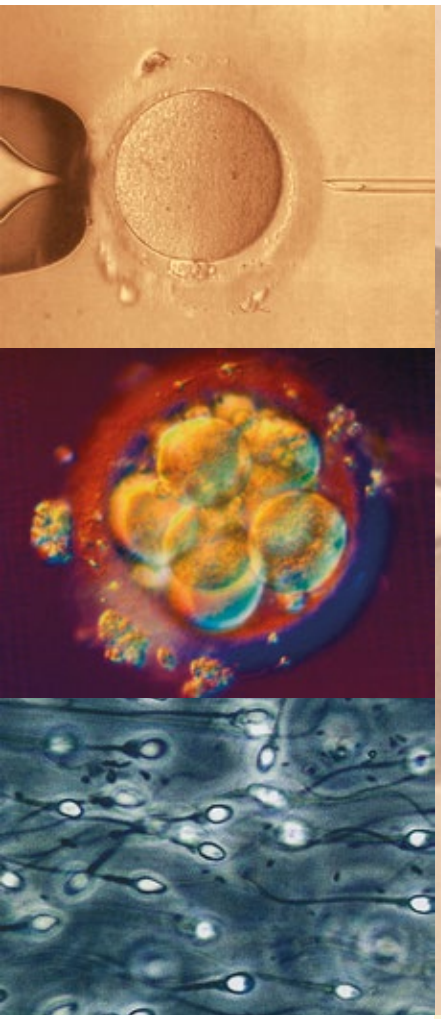

New Technologies for Intrauterine Contraception and Treatment: Design that Fits

Wildemeersch D

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New Technologies for Intrauterine Contraception and Treatment: Design that Fits

D. Wildemeersch

A strategic advantage of intrauterine devices and systems is that, unlike the Pill, they are genuinely 'fit-and-forget'. In use, they are more effective than Pills, particularly in adolescents and nulliparous women, as they have a relatively high continuation of use. The World Health Organization concluded that IUDs can be used and that they are safe for young women, including adolescents. Because adolescents and young nulliparous women contribute disproportionately to the epidemic of unintended pregnancies, suitable long-acting methods of contraception, such as the IUD or IUS, should be advocated as first-line choices for interval, emergency and immediate post-abortal contraception in this population of women.

However, a major drawback is that they do not fit in uterine cavities of many women. Uterine cavities of nulliparous women are usually smaller than those of parous women. As current copper IUDs and the, at present, only available LNG-IUS may not be suitable for many young women, new developments in intrauterine technology, smaller frameless and framed copper and hormone-releasing devices, could help increase the prevalence of use, particularly continued use of this method in women, including in adolescents and nulliparous women, and help reduce the number of unintended pregnancies and induced abortions. **J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 222–6.**

Key words: frameless and framed copper IUD, levonorgestrel IUS, contraception, unintended pregnancy, adolescents, nulliparous women

Introduction: One Design does not fit all Uterine Cavities

Intrauterine devices and intrauterine systems, apart from being long-acting, are particularly attractive as they possess all characteristics listed in Table 1. Moreover, they act locally, avoiding potentially serious systemic adverse effects. A recent re-assessment of the risk of pelvic inflammatory disease attributable to an intrauterine device concluded that intrauterine devices do not affect the fertility of adolescents [2]. Fecundity also rapidly returns to normal after IUD removal [3, 4]. In addition, the levonorgestrel-releasing intrauterine system may offer some protection against sexually transmitted infection [5].

However, uterine cavities differ considerably in size and shape, and the uterus is subject to changes in size and volume during the menstrual cycle [6, 7]. These changes are most pronounced at the time of menses. These individual variations in size and shape of the human uterus are probably greater than variations of the human foot (H.M. Hasson). Therefore, it would be unreasonable to expect one standard-sized IUD/IUS to fit in uterine cavities that differ in size and volume from woman to woman and from time to time in the same woman. Clinical experience has shown that dimensional incompatibility between the IUD/IUS and the uterine cavity can lead to partial or total expulsion, perforation of the uterine wall, pain, unintended pregnancy, and abnormal or heavy uterine bleeding leading to removal of the device [8–10].

Research has shown that if the width of the uterine cavity is too small, side effects and complications are likely to occur. The crossarms of standard T-shaped IUDs are frequently too long for a large number of uterine cavities, as the average transverse diameter of the uterine cavity in the majority of women is smaller than the span of the crossarms of the IUD (Fig. 1). The average transverse diameter of the uterine cavity at the fundal level in nulliparous women between 15 and 34 years of age, as well as in many parous women, is much smaller than the length of the crossarms of most currently used T-shaped IUDs resulting in dimensional problems. The length of the crossarms of the TCu380A IUD and the Mirena® LNG-IUS is 32 mm. The average fundal transverse dimension in nulliparous as well as parous women is only around 25 mm.

Recent 3-D sonography studies compared women with abnormally and those with normally located IUDs with respect to their indication for sonography and found that the proportion of patients whose principal indication for sonogra-

Table 1. Advantages of the IUD/IUS Methods

1. They do not depend on coitus and user motivation and adherence
2. They have the highest effectiveness, continuation rates and satisfaction [1]
3. They do not require frequent visits for resupply
4. They require no additional funding for consistent use once they have been placed
5. They are highly cost-effective
6. They are reversible, with rapid return of fertility after removal

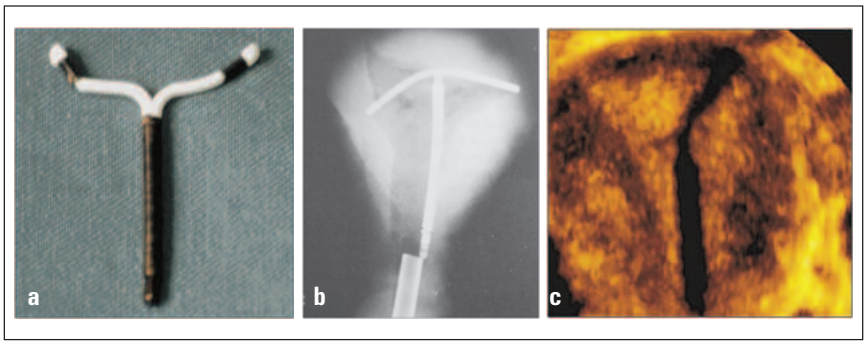

Figure 1. Examples of severe disproportion caused by too long crossarms of copper IUDs **(a, b)** (courtesy of Dr. A. de Castro and Dr. K.-H. Kurz) and of the Mirena® LNG-IUS (3-D sonography) **(c)** (courtesy of Dr. D. Van Schoubroeck).

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Correspondence: Dr. Dirk Wildemeersch, MD, PhD, Outpatient Gynecological Clinic and IUD Training Center, F. Rooseveltlaan 44, 9000 Ghent, Belgium; e-mail: d.wildemeersch@skynet.be

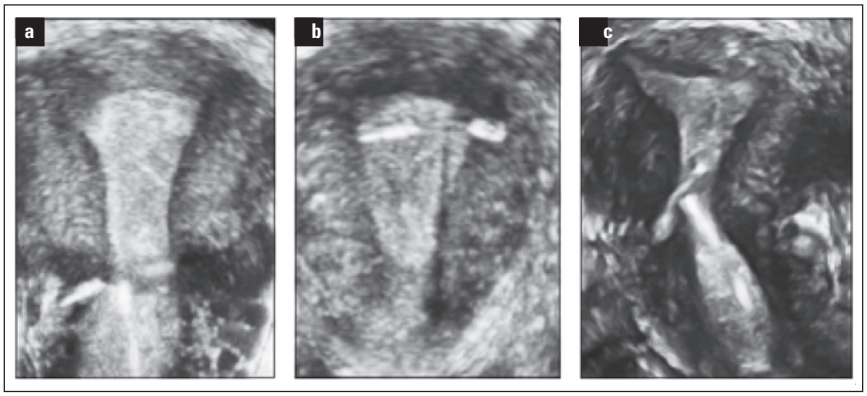
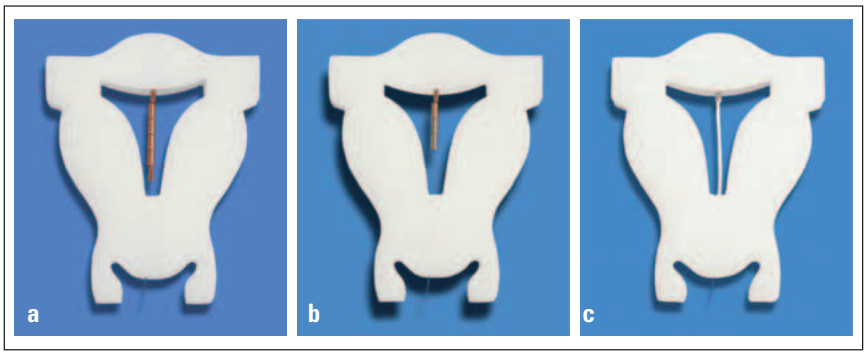
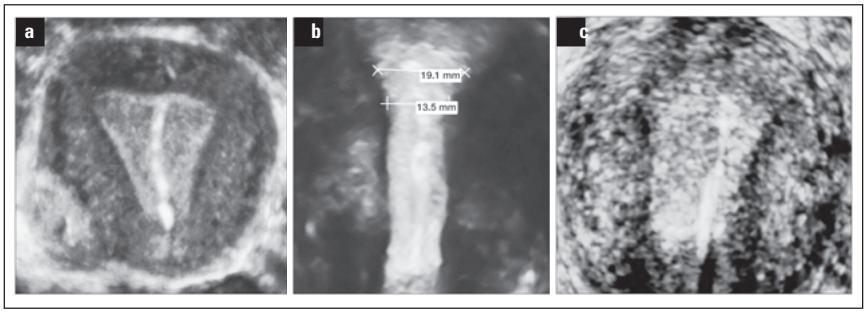


Figure 2. Other examples of severe disproportion caused by too long crossarms of copper IUDs (courtesy of Dr. B. Benacerraf, with permission). These pictures show coronal views of the uterine cavities of three different patients **(a–c)** with intrauterine contraceptive devices abnormally located in different parts of the myometrium or cervix.



Figures 3. The figures above show the GyneFix® 330 IUD **(a)**, the small frameless GyneFix® 200 IUD **(b)** and the FibroPlant® LNG-IUS **(c)**, inserted in a foam uterus. The frameless copper IUD consists of a number of copper tubes attached to an anchoring thread with anchoring knot on top. The drug delivery fiber (1.6 mm in diameter) of the frameless LNG-IUS is attached to the anchoring thread with a stainless steel clip, one cm below the anchoring knot. The latter is inserted in the myometrium of the uterine fundus with a specially designed inserter.



Figures 4. 3-D ultrasound of GyneFix®, illustrating the compatibility of the frameless IUD with the uterine cavity of a parous woman **(a)** (courtesy of Dr. med. P. Villars) and a very narrow uterine cavity (19.1 mm) in a young nulliparous woman **(b)** (courtesy of Dr. S. Jandi) and the frameless FibroPlant® LNG-IUS **(c)** (courtesy of Dr. D. Van Schoubroeck).

phy was bleeding, pain or bleeding and pain were significantly greater in those with an abnormally located IUD, including imbedded IUDs, compared with those whose IUD was not located abnormally on 3-D sonography [11, 12]. It should be noted that standard 2-D sonography is not able to detect many abnormally located IUDs particularly with regard to abnormal location of the sidearms of the IUD. Accurate location of the sidearms is only possible by hysteroscopy and with 3-D coronal sonography, as shown in Figure 2.

A study in current and former Copper T IUD users found a dissatisfaction rate of 34% [13]. The reason for the discontinuation in this study was not available but previous studies showed that heavy bleeding and pelvic pain were the most commonly cited reasons for discontinuing copper IUDs [14–16]. It is therefore logical, as has been confirmed in clinical trials, that harmony between the size of the foreign body and the dimensions of the uterine cavity is essential as regards its acceptability, the occurrence of side effects and the continued use of the method [17–21]. Expulsion rates exceeding 10% during the first year of use have been reported in adolescent nulliparae using traditional IUDs [22, 23]. Recently, a study with the Mirena® conducted in adolescent women in New Zealand found an expulsion rate of 8% after one year of use [24]. The most important factor in reducing IUD side effects, including expulsion, is the elimination of distortion of the uterine cavity (Howard Tatum, inventor of the T-shaped IUD) [25].

The Advantage of Intrauterine Methods that Fit

The frameless copper-releasing GyneFix® IUDs and the frameless FibroPlant® LNG-IUS were developed to optimize harmony with the uterine cavity of parous and nulliparous women in an attempt to reduce the side effects and expulsion rates of conventional IUDs, and consequently, increase continuation of use (Fig. 3).

Figure 4 illustrates the position of the frameless and flexible IUD/IUS in uterine cavities which differ in size and shape as well as the absence of dimensional incompatibility even if the fundal transverse diameter is extremely small.

Different versions of GyneFix® have been clinically tested in large multicenter randomized and non-randomized clinical trials. The high effectiveness has been demonstrated in a randomized comparative study conducted by the WHO and others [26–28]. Failures range from 0.0/100 users to 2.5/100 users (cumulative rates) during the first year up to 10 years of use in published randomized and non-randomized comparative clinical trials [29]. The smaller GyneFix® version has a similar high efficacy [30]. In addition, clinical trials demonstrated, for the first time, the absence of a significant effect of the tiny IUD on menstrual blood loss (Tab. 2) due to the very small size and optimal harmony with the uterine cavity, leaving the cavity totally undisturbed [31]. This is important since abnormal bleeding and pain are the two major reasons for IUD discontinuation [32]. Kivijarvi et al. found clinical anemia in 10% of users of copper IUDs after 12 months exposure and iron deficiency, as judged by the ferritin levels, could be demonstrated

Table 2: Menstrual blood loss evaluation in users of the small GyneFix® 200 IUD. Characteristics of the study group (n = 60, 23 parous and 37 nulliparous women) and analysis by the pictorial bleeding assessment technique, measuring the difference in menstrual score (MS) before and during use of the GyneFix® 200 IUD.

	Age	MS at insertion	MS at last folluw-up
n = 60			
Mean	30.4	116.7	115.2
SD	8.5	52.9	51.1
Median	30.5	110.5	110.0
Range	17–46	28–265	28–260

Wilcoxon matched-pairs signed-ranks test: p = 0.596 (n. s.).

in 20% [33]. In a Swedish study in CuT380A IUD users an increase in MBL was shown which ranged between 50 and 60% [34]. This study is comparable with previous reports regarding the increase in MBL associated with the use of a copper IUD. Attempts to reduce menstrual bleeding in TCu380A users with the use of nonsteroidal anti-inflammatory drugs for analgesia yielded mixed results [35]. Anti-inflammatory drugs were also unsuccessful in reducing the removal rate due to cramping pain [36].

As a consequence of the harmonious relationship of the frameless GyneFix® IUD with uterine cavities with a different transverse diameter, removal rates for abnormal bleeding and pain complaints have been low (< 1/100 women per year at 3 years), particularly with the smaller version. Consequently, high continuation rates were recorded (over 90% at 3 years) which continued to be high during the years thereafter. Contraceptive discontinuation rates of conventional IUDs and the Mirena® LNG-IUS are known to be higher among adolescents than for adult women. The Mirena® discontinuation rates in females aged 18–25 years was 20% at one year, with pain as the leading cause for removal [37]. This corresponds with an IUD/IUS study conducted in nulliparous women in the UK [38]. Earlier studies also reported LNG-IUS discontinuation rates because of pain and bleeding problems that are higher in the younger age groups [39, 40]. Similarly, heavy menses and dysmenorrhea are the most frequent reasons for the removal of the TCu380A in the first year after insertion [41].

The length of the IUD does not seem to be important clinically, unless there is a great difference between cavity length and the length of the stem of the IUD/IUS. It appears, therefore, that the main factor related to dimensional or spatial compatibility of the IUD/IUS with the uterine cavity remains the width or transverse diameter of the uterine cavity. 3-D sonography provides useful information on the location of the IUD/IUS and enables proper imaging of the device and the relationship between the IUD/IUS and the uterine cavity. Visualizing the acoustic shadow of the IUD/IUS provides a useful additional modality in cases of difficult visualization [42, 43].

There is No Increased Risk of Perforation with the Frameless, Anchored IUD/IUS

Of the 5346 insertions (4808 interval and 543 immediately post-abortal) conducted in clinical trials with the frameless copper-releasing IUD, there were no perforations [26]. In the two large post-marketing trials conducted in Belgium and Spain with GyneFix® in over 12,000 women, the rate was 1.2–2.0/1000 insertions which is similar to the quoted perforation rate occurring with traditional IUDs [44]. The risk of perforation can be reduced by proper training (see below) and by visualization of the anchor by ultrasound. The manufacturer of the frameless GyneFix® and frameless FibroPlant® LNG-IUS incorporated a small metal particle in the anchoring system rendering the anchor highly visible on ultrasound examination (Figs. 5, 6) (patent pending). This allows assessment of the proper position of the anchor in the muscle of the uterine fundus following insertion and at follow-up. In the rare event of perforation of the uterine serosa, or in case of doubt, the frameless IUD/IUS can be removed and a new insertion can be performed immediately or at a later date.

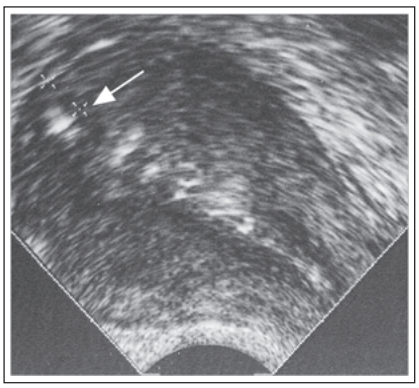


Figure 5. 2-D sonography of the new "visualized" anchor (See arrow). The anchor is located 6 mm from the serosa of the uterus.

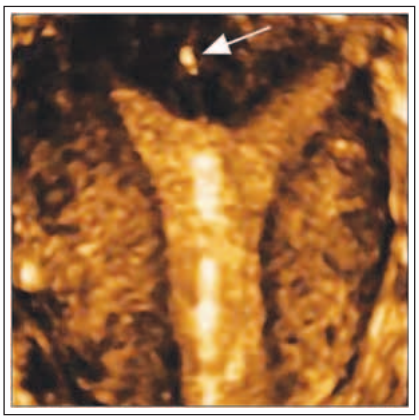


Figure 6. 3-D sonography of the new "visualized" anchor (See arrow).

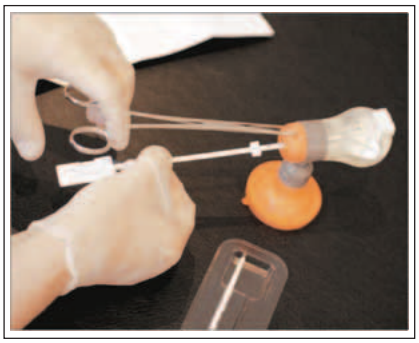


Figure 7. Home Uterine Trainer (HUT®) suitable for home-training of the frameless IUD/IUS insertion technique.

Training Aspects

As the frameless technology is new, familiarity with the insertion procedure may be acquired only after a number of insertions have been completed, depending on the skill of the provider. Experience has shown that insertion failures and expulsions, in parous as well as nul-

liparous women, can be minimized to very low rates if providers attend a training course organized by the manufacturer. Proper training is essential to properly insert the GyneFix® and will result in optimal performance and high continuation of use. Following training, providers can become proficient by conducting training by themselves in an appropriate "home" uterine model (Fig. 7) before they start insertions in their patients.

Conclusion

Many unintended pregnancies and induced abortions can be avoided by providing intrauterine devices that cause a high continuation of use. Nulliparous women who need or want a non-systemic contraceptive option may benefit from a smaller framed IUD/IUS or from the frameless copper or a frameless LNG-releasing system. Among nulliparous women, where the issue of incompatibility may be more pronounced, clinical studies suggest the high tolerance and high continuation rates of the frameless IUD and IUS [29, 45]. In addition, if properly inserted, expulsion of the IUD/IUS is rare.

Young men and women are a highly vulnerable population. They deserve to be informed and to have access to high-quality and effective reproductive health care assistance. High-performing, forgettable, long-acting, reversible, and well-tolerated contraceptives, with a high continuation of use are needed to reduce unintended pregnancies in young women [46].

However, outdated perceptions about appropriate patient candidate for long-acting methods among health care providers continue to negatively impact their use. These myths should be vigorously dispelled.

Finally, the gynecological examination, and insertion of an IUD, in young nulliparous women and adolescents, may be challenging. IUD fitting should be done with extreme care and with attention to comfort and pain relief as pain scores may be quite high with vagal reactions [34, 47]. The use of misoprostol may be useful to maximize comfort and facilitate IUD insertion by softening the cervix and reducing the chance of complications such as perforation, pain and bleeding [48].

Acknowledgment

Dr. D. Wildemeersch is grateful to a large number of colleagues in Belgium and abroad for being investigators and

co-investigators in the clinical studies conducted with the frameless and framed IUDs/IUSs.

Conflict of Interest

Dirk Wildemeersch, MD, PhD, is a Belgian gynaecologist and Medical Director of Contrel Drug Delivery Research, an organization which was established to manage clinical research and to develop and study innovative drug delivery technologies, aimed at finding improved methods for prevention and treatment of gynecological conditions, improvements to birth control methods, and higher levels of safety, user acceptability, compliance and quality of life for women. Contrel is the manufacturer of GyneFix®, FibroPlant® and Femilis®. The research organization also provides insertion training for doctors. The funds generated are used for conducting further research and to participate in humanitarian projects.

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