Clinical Perspective

Considering the risks and benefits of intrauterine devices: should clinician advice now be changed?

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Practice points

- There are no restrictions concerning age or parity with respect to the insertion of any kind of intrauterine contraceptive (IUC).
- There is no difference in the pregnancy rate between adolescents and adult women either with the copper-releasing intrauterine device or the levonorgestrel-releasing intrauterine system.
- Insertion is simple with both types of IUC in nulligravidae and parous women, with insertion failure due to cervical stenosis constituting a rare event.
- Fear of pain represents a barrier to the use of IUCs and has been reported to occur prior to placement, during the procedure and after the procedure.
- The risk of expulsion of the IUC is similar in nulligravidae and parous women.
- Uterine perforation is a rare event; however, the risk is higher when the device is inserted by healthcare providers with less experience in the insertion technique.
- Pelvic inflammatory disease is caused by sexually transmitted infections and not by the use of the IUC.
- The use of an IUC does not cause infertility and, after using the device, return of fertility is similar to that of never users.

SUMMARY

Intrauterine contraceptives (IUCs) are the most widely used contraceptive method in the world, the two most common models currently in use being the TCu380A intrauterine device and the levonorgestrel-releasing intrauterine system. IUCs and subdermal implants are referred to as ‘long-acting reversible contraceptives’ because they provide

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contraception for at least 3 years with a single intervention. Both IUCs and the contraceptive implant have very low rates of contraceptive failure, these rates being similar in women over and under 21 years of age. They are safe, with few side effects, have a high continuation rate and can be used irrespective of age or parity. However, even now, many healthcare professionals discourage the use of these devices by adolescents, young women and nulligravidas, although the WHO makes no restrictions in this respect. IUCs represent an excellent tool for preventing unplanned pregnancy and should be considered as a first-line contraceptive choice for any woman with no medical contraindications.

Intrauterine contraceptives (IUCs) are the most prevalent contraceptive method in use worldwide. Models currently in use include copper-releasing intrauterine devices (IUDs), of which the most common model worldwide is the T-shaped TCu380A, and the levonorgestrel-releasing intrauterine system (LNG-IUS). IUCs, together with contraceptive implants, are considered ‘long-acting reversible contraceptives’ (LARCs) or ‘ forgettable contraceptives’ because they provide contraception for at least 3 years of use with only one intervention and do not depend on user compliance [1]. In fact, the TCu380A IUD is approved for 10 years of use; however, reports have shown its efficacy can last for 15 and 20 years [2,3]. The approved duration of use of the LNG-IUS is up to 5 years [4]; nevertheless, it has a wide timeframe during which replacement can be made [5].

It has been well established that the pregnancy rate with LARCs is lower than that found with non-LARC methods. In addition, when young adult women under 21 years of age were compared with women over 21 years of age, this low pregnancy rate was similar in both groups [6], which could be explained by the fact that these contraceptive methods do not depend on women’s daily or monthly compliance. In fact, pregnancy rates with both models of IUCs are similar or lower than those found with female sterilization [6–8]. Continuation rates for both IUCs at 3 years were better than the continuation rates found in women using non-LARC methods. In addition, the repeat occurrence of an unplanned pregnancy was found to be less likely in users of the copper-IUD and the LNG-IUS compared with users of combined oral contraceptives (COCs), patch or vaginal ring [6].

Despite the low pregnancy rate, the high continuation rate and the low frequency of side effects reported with IUCs [4,9], the number of women using the most common IUCs remains small in many countries, albeit the prevalence of use varies greatly from country to country [10]. For example, the 2008 National Survey of Family Growth in the USA [102] reported that only 5.5% of women using contraception stated that they used an IUD [103].

In a recent USA-based study with 503 women aged 16–24 years [104], 77% wanted a contraceptive method that does not require them to have to remember it every day or that has to be used during sex. However, only 7% used LARC methods or depot medroxyprogesterone acetate injections, and only 1% of the remaining women were aware of these methods. Furthermore, 77% of the women interviewed who were using COCs had forgotten at least one pill.

One of the main reasons for the underutilization of IUCs is the many restrictions imposed by healthcare professionals (HCPs) as a consequence of the myths and misconceptions that surround the use of these contraceptive methods, principally concerning their use in women and adolescents who have never been pregnant and in young women in general. Nevertheless, in view of current evidence on the efficacy and safety of IUCs, it is important that clinicians are advised that it is time for change [10].

**Restrictions imposed by HCPs**

The principal reasons given for the limited use of IUCs in the USA and UK refer to the misperceptions and misgivings of HCPs regarding the eligibility criteria for IUCs, particularly with respect to the age and parity of the potential users [10–12]. One USA-based survey, in which members of the American College of Obstetrics and Gynecology (ACOG) were interviewed, showed that 68% of physicians would not recommend copper-IUDs to nulliparous women, although 95% reported having a positive attitude towards the IUD and 95% were well informed on the efficacy and safety of these devices [13].
In another study involving approximately 800 family planning professionals based in California (USA), just under 50% of the professionals who participated in the interview stated that nulliparous women, adolescents, and women who had pelvic inflammatory disease (PID) within the previous 5 years, were not candidates for an IUC. Women in the postpartum or postabortion periods were also not considered eligible to use these devices [14]. Likewise, a similar Australia-based survey involving 701 fellows of the Royal Australian and New Zealand College of Obstetricians and Gynecologists reported that only approximately one-third (39.1%) and two-thirds (69.4%) of the HCP interviewed believed that the copper-IUD and the LNG-IUS, respectively, were appropriate for nulliparous women [15].

In addition, a survey conducted in the UK showed that only approximately 2% of HCPs reported that they might recommend an IUD to an adolescent nulliparous woman [12]. In the aforementioned study, conducted with ACOG members in the USA [13], when doctors were asked what makes women eligible for an IUC, only 62.0% agreed that these devices are appropriate for nulliparous women, while 30.7% agreed that they were appropriate for adolescents, 45.3% for a woman with a history of a sexually transmitted infection (STI) in the past 2 years and 36.5% for a woman who had PID in the past 5 years. Only 49.6% of these HCPs reported that they would offer an IUC to a single, monogamous adolescent with one child, and 19% said they would offer this form of contraception to an adolescent nulligravida.

The misgivings of HCPs regarding the use of IUCs in nulligravidas may originate from when the TCu380A IUD was first introduced onto the USA market in 1988. At that time, it was recommended that eligible women should have had at least one child; however, this requirement was removed in 2005 and nulliparous women are now considered eligible to use the TCu380A IUD [105]. However, the package insert that accompanies the LNG-IUS still recommends (although it is not mandatory) that candidates for the use of this device should be parous [106], despite the fact that the eligibility criteria established by the WHO classifies any IUC as category 2 both for nulligravidas and parous women [107]. These restrictions have resulted in a scarcity of studies in the scientific literature on the use of IUCs in nulligravidas, adolescents and young women, leaving HCPs with insufficient evidence to change the pattern of use of these devices in these specific groups of women. However, adolescents and young women are those at a high risk of unplanned pregnancy and IUCs represent an excellent strategy for increasing effective contraceptive use.

- **Lack of training in IUC insertion & management**

It is important to point out that the restrictions in providing IUCs may reflect a lack of training in many medical schools, particularly during medical residency. To provide IUCs, physicians and other HCPs must be willing to offer these contraceptives to all women and insert them, the only exceptions being the restrictions defined in the medical eligibility criteria [107]. A study conducted in St Louis (MO, USA) questioned HCPs on the subject of training and their attitudes with respect to IUCs [16]. Results showed that 36% of HCPs had received no training in IUC insertion during their residency or, in the case of nurses, at advanced clinical practice courses. In addition, the HCPs who were trained at Catholic institutions were less likely to have received training in IUC insertion during residency compared with HCPs who trained at secular institutions.

- **Difficulty at insertion & pain during the procedure**

One of the principal concerns of HCPs with respect to IUC insertion refers to the myth that insertion is difficult, particularly in nulligravidas and adolescent women. This myth originated from the idea that the cervical canal or internal os is narrow in these populations of women, making insertion more difficult or painful. Nulliparous women have been reported to have a narrower internal cervical os and/or a narrower cervical canal, and a higher failure rate or difficulty at insertion has been described in nulliparous women compared with parous women [17]. However, several studies have shown that insertion of a copper-IUD or LNG-IUS in nulliparous women is just as safe and simple a procedure as in parous women [18–20], with the advantage of a high continuation rate.

A study conducted in 24 sites in Sweden evaluated the insertion procedure of the LNG-IUS in 224 nulliparous women including
181 nulligravidas [21]. The insertions were performed mostly by midwives and were classified as easy by 72% of HCPs. The insertion failure rate was only 2.7%, and 72% of the women who inserted an LNG-IUS considered the procedure moderately painful, with only 17% reporting it was severely painful. In another study [19], 315 questionnaires were sent to HCPs who had inserted an LNG-IUS in nulligravidas. These professionals reported a relative risk (RR) of 2.0 (95% CI: 1.2–3.2) for a difficult insertion in nulliparous women compared with parous women, while the number of insertions carried out by the HCP. Those HCPs who had performed fewer insertions were more likely to experience difficulty at insertion (RR: 2.2; 95% CI: 1.6–3.1).

Another study compared the ease of insertion and failure rates of the LNG-IUS in two cohorts: one group of nulligravidas and another of parous women [22]. The principal results showed ease of insertion in almost 80% of the women in both groups and insertion failure in only 0.4%, with no differences between the nulligravidas and the parous women. The continuation rate at the end of the first year was almost 90% in both groups of nulligravidas and parous women.

Fear of pain during insertion may play a role in whether or not women choose to use an IUC [23,24]. In addition, HCP’s misgivings regarding painful and difficult insertions may make them reluctant to offer IUCs as a contraceptive method or to counsel women on IUCs, particularly when the woman is a nulligravida and/or adolescent. Pain at IUC insertion has been reported to be greater in nulliparous women [25]; however, this remains a controversial issue. In a prospective study conducted with 117 nulliparous women [26], 62% reported that the pain at IUC insertion was similar to that experienced during menstruation and 75% of the women were still using the device for up to 1 year, which may be an indicator of the high levels of satisfaction that have been reported with this method. Furthermore, in a study in which most of the women were parous, almost 89% reported either no pain or mild or moderate pain during IUC insertion, with severe pain being reported by only approximately 11% [27].

Risk of expulsion
One of the principal concerns of HCP and women regarding IUCs is the risk of inadvertent expulsion, since this may lead to an unplanned pregnancy. Despite the body of evidence on the expulsion rates of different IUCs, controversies remain regarding which women are more likely to experience expulsions. Higher expulsion rates have been reported in nulliparous compared with parous women using the TCU380A IUD [28]; however, other authors have reported conflicting findings [29–31].

One hypothesis that has been proposed to explain expulsions of any model of IUC refers to the length of the uterine cavity. If we take into account that the TCU380A IUD is 3.6 cm in length and the LNG-IUS is 3.2 cm, the association between expulsion and uterine size may be different for the two IUC models. This is one of the reasons why many HCPs are reluctant to insert an IUC in women with a total uterine length (from the external os to the distal end of the fundus) of less than 6.0 cm or greater than 9.5 cm, although some authors have failed to find any association between expulsion rate and the length of the uterine cavity [32,33]. In addition, one of the reasons why HCPs are reluctant to insert an IUC in a woman whose uterine length is less than 6.0 cm is the manufacturer’s recommendations on the package insert, which informs that the risk of expulsion is greater in these women [105,106].

There have also been speculations regarding the substantial difference in uterine length between nulligravidas and parous women, hence nulligravidas needing shorter IUCs owing to a shorter uterine length constitutes yet another myth. Due to the controversies regarding the need for smaller or shorter IUCs that could reduce the expulsion rate, one study used uterine sounding and ultrasonography to assess the length of the endometrial cavity in 260 nulligravidas and 310 parous women [34]. The principal findings demonstrated that the mean difference in length was only 0.28 cm, when comparing uterine sounding and ultrasonography.

In addition, the mean length of the endometrial cavity (± standard error of the mean) was 3.84 ± 0.03 cm in nulligravidas and 4.25 ± 0.03 cm in parous women according to uterine sounding, and 3.70 ± 0.03 and 3.84 ± 0.03 cm, respectively, according to ultrasonography [34]. Consequently, the mean length of the endometrial cavity was greater than the length of the TCU380A and the LNG-IUS, although it is important to take
into account that in almost 33% of the women endometrial length was less than 3.2 cm, which is the length of the LNG-IUS.

Dueñas et al. conducted a retrospective study to evaluate 461 users of IUDs, including 129 nulliparous women. These authors reported no difference in the expulsion rates between nulliparous and parous women [35]. Although the review conducted by Hubacher regarding the performance of copper-IUDs in nulliparous women found that in 13 out of the 20 studies evaluated, expulsion rates were higher in nulliparous women [22], the current TCu380A IUD was evaluated in only one of these studies. In addition, another study conducted with the LNG-IUS reported an expulsion rate of 3.7% in nulligravidas and 4.6% in parous women, with no statistically significant difference between the two groups [22].

In a recent study that evaluated whether the expulsion rates with the TCu380A IUD and the LNG-IUS correlated with the length of the endometrial cavity, 235 nulligravidas and parous women received one of the two models of IUC and were followed-up for up to 1 year [36]. Uterine sounding and ultrasonography were used to measure the length of the uterine cavity. The two expulsions observed in users of the LNG-IUS did not occur in women with an endometrial length of less than 3.2 cm. In users of the TCu380A, IUD expulsions occurred in three women (4.8%) whose endometrial length was less than 3.6 cm and in five women (6.0%) with an endometrial length of 3.6 cm or more. Furthermore, when the endometrial cavity of the ten women in whom expulsion of the IUC occurred was assessed by ultrasonography, the length was found to be 3.9 ± 0.3 cm compared with 3.9 ± 0.0 cm in those women in whom expulsion did not occur.

In a study conducted by the WHO [37], the cumulative expulsion rates in users of the TCu380A IUD ranged from 2.5 to 6.1% up to the first and eighth years of use, respectively, with higher rates being associated with a lack of experience in the HCPs who inserted the device. However, it must be taken into account that women who expel an IUC and have a replacement device inserted are more likely to experience expulsion again, irrespective of the IUC model [38–39]. One study showed net cumulative re-expulsion rates at 6 and 12 months of 21.7 and 31.4%, respectively [40].

### Risk of uterine perforation

Another major concern of HCPs when inserting any model of IUC is the risk of uterine perforation. However, the risk at the time of IUC insertion has been reported to range from 0.0 to only 1.3% [40]. Apparently, the risk of uterine perforation may be higher in nulliparous women compared with parous women; however, to the best of our knowledge, there are no comparative studies in which uterine perforation rates were compared between nulliparous and parous women.

If the IUC strings are missing at the external cervical os at any follow-up visit, this may be an indication of uterine perforation; however, it may also be an indicator of unnoticed IUC expulsion. If the woman reports pain in the lower abdomen or pelvis, if a previous amenorrheic user of the LNG-IUS reports normal bleeding occurring during use of the device or if an accidental pregnancy occurs, the HCP should suspect uterine perforation. However, cases have been reported of women with uterine perforation and no complaints [41]. In addition, perforation should be suspected if the HCP who performed the insertion was in training, if the insertion was difficult, if dilatation of the cervix was required, if cervical stenosis was present, if the woman has a history of cesarean section, if she experienced severe pain at insertion and/or presents with an extremely retroverted or retroflexed uterus [42]. Nevertheless, it is extremely important to follow the manufacturer’s instructions to avoid or reduce the risk of perforation [43–45].

### Risk of pelvic infection & future infertility

One of the main concerns from the point of view of the HCP is the possibility that the use of an IUC could provoke PID, leading to infertility in the future when inserted in adolescents and/or nulligravidas. In the aforementioned study in which HCPs were interviewed [16], almost all of the respondents (98.5%) agreed on the safety of IUCs; however, a contradictory finding was that 29% of the HCPs reported that IUCs increase a woman’s risk of developing PID, even outside the period immediately following insertion.

These concerns arose mainly from the use of the IUD rather than the LNG-IUS and particularly following use of the Dalkon Shield IUD many years ago. This IUD is no longer available; however, a relationship was reported between its use and an increased risk of PID. This may be due to the fact that the device had a
multifilament string that facilitates the ascension of microbes into the female genital tract [46]. This IUD was the subject of many lawsuits [47]. However, there is sufficient scientific evidence that the use of modern IUCs, including the copper-IUD and the LNG-IUS, offers no risk during use; however, the risk of infection is elevated in the first 21 days after insertion before returning to baseline risk [48].

Neither copper-IUD users nor LNG-IUS users are at any increased risk of PID and this statement is also valid for nulligravidas [49]. It has been shown that modern devices with monofilament strings do not increase a woman’s risk of PID. The risk of PID is higher around the time of insertion, particularly in the first 20 days after insertion [50–53] and this risk is related to previous cervical infections, principally Chlamydia trachomatis. After that period, the risk of PID is associated with unprotected sexual intercourse and the consequent risk of STI, which is the main reason to develop a PID. Nevertheless, rates of PID appear to be lower in users of the LNG-IUS compared with copper-IUD users [54].

Another retrospective study assessed the complication rates of 194 users of either the TCu380A IUD or the LNG-IUS [55]. Although 33% of the users had a history of STI, no increased risk of PID was found. In addition, in a retrospective study conducted with the TCu380A IUD and the LNG-IUS in adolescents and young adults, the risk of PID was lower in users of the LNG-IUS [56].

PID poses an additional risk to future infertility, and this is a concern mainly in the case of women who have not yet completed their family and principally nulligravidas. This concern constitutes another limitation to the use of any IUC. However, there is no evidence that the use of the copper-IUD or the LNG-IUS increases the woman’s risk of infertility in the future. Regarding the return of fertility, albeit there is evidence that there is no delay following the use of modern models of copper-IUDs or the LNG-IUS [57], the evidence is still controversial [58]. In a UK-based report [59], 558 nulliparous women participated in a study that evaluated the return of fertility after the use of an IUD. The authors showed that among women who discontinued use of IUD or barrier methods, 39 and 54%, respectively delivered after 1 year (p = 0.002). Furthermore, it was observed that long-term use of IUDs was associated with decreasing fertility (p = 0.005) and 79% of women who used an IUD for 78 months or more delivered at 36 months in comparison to 91% of women who used the IUD for a short time.

One case–control study with 1895 women, including 358 women with primary infertility due to tubal obstruction, 953 infertile women without tubal obstruction and 584 pregnant women, tested for C. trachomatis antibodies in the blood of all the participants [60]. When infertile women with tubal obstruction were compared with the infertile controls, the odds ratio (OR) for tubal obstruction associated with a history of copper-IUD use was 1.0 (95% CI: 0.6–1.7) and when compared with primigravidas, the OR was 0.9 (95% CI: 0.5–1.6). In addition, infertility due to tubal obstruction was not associated with the duration of IUD use; however, positivity for C. trachomatis antibodies was associated with infertility.

In another case–control study involving 215 women who were infertile due to tubal obstruction, a history of pelvic surgery and alcohol consumption were shown to be factors significantly associated with the risk of infertility caused by tubal obstruction [61]; however, in women with secondary infertility, a history of pelvic surgery and the number of lifetime sexual partners were found to be significant risk factors [61]. A history of IUD use was not associated with future tubal infertility.

In fact, the probability of becoming pregnant following removal of any IUD is similar to that observed in the general population of women not using any contraceptive method. One study evaluated the return to fertility in 372 women who interrupted the use of different contraceptive methods, including the LNG-IUS and the copper-IUD, because they wished to become pregnant [9]. Life-table analysis showed 12 and 24 month pregnancy rates of 80 and 92/100 women-years, respectively. It is important to note that 34% of LNG-IUS users and 43% of copper-IUD users became pregnant within 3 months of discontinuing the method, with younger age at removal being the most important factor for predicting a fast return to fertility.

In a multicenter study conducted in several European countries, the LNG-IUS was compared with the Nova-T® copper-IUD with respect to women’s return to fertility after discontinuation of the device [62]. A total of 209 women (138 users
of the LNG-IUS and 71 users of the copper-IUD), who discontinued use of the device because they wished to become pregnant, were followed-up for 2 years after removal. The gross cumulative pregnancy rates were 71.2 and 79.7/100 women at 12 and 24 months, respectively, for the copper-IUD and 79.1 and 86.6/100 women at 12 and 24 months, respectively, for the LNG-IUS. There was no statistically significant difference between the two IUCs. In addition, 96% of the pregnancies in both groups occurred during the first year following removal.

- Use restrictions for adolescents & young adults

Although IUCs have been shown to be highly effective with few side effects, according to the 2010 USA National Survey of Family Growth only 2% of women of 15–24 years of age have ever used these contraceptive methods [63]. Due to the wide discrepancy between the benefits offered by IUCs and the low prevalence of use of these devices, particularly in adolescents, ACOG released a committee opinion stating that IUC is a first-line agent for preventing unplanned pregnancy in both nulliparous women and adolescents [64]. In addition, NICE released a document in 2005 stating that there are no restrictions to IUC use based on age or parity [108]. A similar statement was released in 2009 by the WHO stating that the benefits of IUD use generally outweigh the risks in women from menarche onwards, and that the IUD was designated a category 2 contraceptive method for adolescents [107].

It is probable that the concerns regarding the use of any IUC in adolescents arose partly because of the scarcity of information on the subject in the medical literature. However, due to the number of adolescents who become pregnant [109], the question is why should the IUC be denied to adolescents, even parous adolescents? One study evaluated the clinical performance of the TCu 200B IUD (an IUD no longer on the market) in a cohort of 995 parous adolescents, with each teenager being compared with a control 10 years older with identical parity [65]. The results showed that pregnancy rates, expulsion rates and discontinuations due to bleeding and/or pain were higher in the group of adolescents; however, removals due to infection were in the same proportion with no differences between the adolescents and adults.

On the other hand, another study [66] conducted with 1603 nulliparous women (40.6% were ≤20 years old), using three different models of copper-IUDs including the TCu380A IUD, reported a continuation rate at the end of the first year of 81.9/100 women-years. Furthermore, other authors, in a review with data from different studies, have shown a cumulative continuation rate of 55.7/100 women-years of use at 2 years with the TCu380A IUD in nulliparous women and an average (between the different studies) annual rate of 74.6/100 women-years of use [29].

Another study with 179 adolescents of up to 19 years of age who received an LNG-IUS reported an expulsion rate of 8% and a 1-year continuation rate of 85% [67]. Suhonen et al. evaluated the clinical performance of IUDs compared with COCs in young women of 18–25 years of age [18]. Approximately 20%, however, were not nulligravidas. The IUD was found to be well tolerated, with a continuation rate of 79.8/100 women-years of use at the end of the first year in these young women.

In a review study conducted at three US-based clinics, the authors reviewed the charts of 223 women under 21 years of age who received a TCu380A IUD (n = 11; 4.7%) or an LNG-IUS (n = 222; 95.2%) [56]. Only 71 women (30%) were nulliparous and 90% of the insertions were performed for contraceptive purposes. Dilation was required in only 4.3% of the women, while difficulty at insertion was recorded in 1.3% and insertion failure in a similar proportion (1.3%). In addition, the risk of expulsion was found to be higher in nulligravidas (RR: 10.6; p = 0.006), while women with a history of previous reproductive tract infection were found to be at a greater risk of infection. The 5-year continuation rate was 50% for women under 18 years of age at insertion and 71.5% for those of 18–21 years of age.

In another retrospective study [67], the authors evaluated 307 women under 19 years of age, 77.5% of whom were nulliparous. IUDs were successfully inserted in the majority of the women (n = 296; 96.4%), while expulsions within the first year of follow-up accounted for 2.9% (five out of 172). There were no statistically significant differences between nulliparous and parous adolescents with respect to any of the other reasons for removal. Although no pregnancies occurred, it is important to note that PID was diagnosed in eight women (4.6%). The authors
concluded that although the discontinuation rate was higher than rates reported for adults, it was lower than those found with other contraceptive methods in adolescents [68].

- Lack of awareness regarding the noncontraceptive benefits of IUCs

Contraceptive methods were developed to provide protection against unplanned or undesired pregnancy. However, since the introduction of the first COC 50 years ago, many noncontraceptive benefits have been reported. Nevertheless, many users, potential users and even HCPs remain unaware of these benefits or, if aware of them, HCPs fail to communicate these benefits to their patients.

One of the well-established benefits of the copper-IUD and potentially of the LNG-IUS is a reduction in the risk of endometrial cancer [69–72]. In a recent review [69], the authors identified nine case–control studies and one cohort study, all of which showed a protective effect against endometrial cancer in women who had used an IUD at any time (pooled adjusted OR: 0.6, 95% CI 0.4–0.7). No association was found between the type of IUD and the histologic type of cancer. In addition, three studies failed to find any link between IUD use and hydatidiform moles or malignant sequela. Regarding the LNG-IUS, there are several publications on the successful treatment of endometrial cancer and endometrial hyperplasia. However, the use of LNG-IUS as a preventive strategy of the disease is still speculative, albeit there are authors in favor of the use of the LNG-IUS as therapy to prevent endometrial cancer [73].

Regarding the association between IUD use and the risk of cervical cancer, this remained a controversial issue until last year [74]. A study evaluated several large epidemiological studies on human papillomavirus conducted in various countries with different populations and assessed the association between IUD use and the risk of cervical human papillomavirus infection and cervical cancer. After adjusting for confounders, these authors found an inverse association between the use of IUDs and cervical cancer (OR: 0.55; 95% CI: 0.42–0.70), including a protective effect against squamous-cell carcinoma (OR: 0.56; 95% CI: 0.43–0.72), adenocarcinoma and adenosquamous carcinoma (OR: 0.46; 95% CI: 0.22–0.97). The authors suggested that the protective effect of the IUD works through cellular immunity triggered by the IUD, among other factors.

With respect to the LNG-IUS, it has been well established that this device represents an excellent option for the medical treatment of women with heavy menstrual bleeding (HMB) [75,76], which is one of the most common complaints in gynecology, the pathology for which use of the LNG-IUS has been most intensely evaluated as an alternative to hysterectomy. Chronic HMB is a health problem that affects women of reproductive age, many of whom also require contraceptive protection. Many studies have shown that the use of the LNG-IUS leads to a reduction in the number of bleeding days and bleeding episodes and in the amount of bleeding, even in women with hematological disorders and those in use of anticoagulants [27,75,76].

In women who were waiting for a hysterectomy [77], surgery was cancelled after 6 months in 64.3% of women in the LNG-IUS group and 14.3% of the controls. When women with HMB were randomized to an LNG-IUS or hysterectomy [78], 48% of the women allocated to the LNG-IUS remained in use of the device 5 years after insertion, thus avoiding surgery. LNG-IUS is also a common complaint in women with hematological diseases and/or women receiving warfarin for a thrombotic disorder [79], and the LNG-IUS also represents an option for these women because, in addition to the contraceptive protection offered by the device, it reduces menstrual blood loss and provokes amenorrhea in a high proportion of women [80]. In addition, this device has been used off-label to treat pain-associated endometriosis, with excellent results; however, there have been few publications so far on this subject [81–84].

It is important to take into account that nulligravidae may also request the LNG-IUS not only for contraception, but also for the treatment of HMB. In the Brazilian study conducted with cohorts of nulligravidae and parous women, HMB constituted an additional reason for women to use the LNG-IUS, either idiopathic HMB or HMB following weight loss after bariatric surgery or as a result of fibroids [22]. The improvement in menstrual bleeding patterns or the amenorrhea induced by the device may prevent the development of iron deficiency anemia [85].
Conclusion
Presently, the number of women of reproductive age around the world who need effective LARCts is substantial, and the proportion of sexually active women who are nulliparous or nulligravida is also high and rising steadily. This is occurring because many women choose to remain childless, or delay the birth of their first child, and because cesarean section rates have increased. IUCs are an excellent tool for reducing the rate of unplanned pregnancies or undesirable pregnancies, and age and parity must not be used as a reason for refusing women the opportunity to use a copper-IUD or LNG-IUS should they wish to do so. Over recent years, the number of articles in the scientific literature on the need to put IUC use into its true perspective with respect to the contraceptive effectiveness with the new smaller LNG-IUS may have some benefit and the inserters who performed the procedure easier, principally in nulligravidas. The reason may be unsuccessful in inserting the device currently available on the market. The development of these new LNG-IUS was similar to that found with the device currently on the market.

Although insertions were less difficult with the two smaller LNG-IUS, the authors failed to differentiate between nulligravidas and parous women; however, acceptors of the new smaller LNG-IUS reported less pain at insertion. In our opinion, this is probably the most important finding because fear of pain could reduce the number of women opting to use an IUC, principally if we consider that the actions taken to reduce pain are unsuccessful. We believe that the development of these new LNG-IUS is welcome, particularly because lower-dose LNG-IUS may have some benefit and the inserters are narrower, which may make the insertion procedure easier, principally in nulligravidas. The large Phase III trial currently being conducted by Bayer Healthcare (NJ, USA) is still ongoing.

Future perspective
The length of the most common copper-IUD, the TCu380A, is 3.6 cm, while that of the LNG-IUS is 3.2 cm. Many HCPs are concerned that these IUCs are not appropriate for all women, principally nulligravidas, since these women have small endometrial cavities and consequently may be more prone to expulsions and side effects compared with parous women.

There is only one model of the TCu380A IUD and also only one model of the LNG-IUS on the market, the former being of 3.6 cm and the latter of 3.2 cm in length. The current LNG-IUS releases 20 µg of LNG per day. Some HCPs call for smaller IUCs with the argument that the current IUCs are inappropriate for nulligravidas, despite the body of evidence showing that both devices are indeed appropriate for nulligravidas, as demonstrated in this review.

Recently, Gemzell-Danielsson et al. presented data on the clinical performance of two new low-dose LNG-IUS and compared them with the device currently available on the market (LNG-IUS12). The development of new devices that release low doses of LNG is based on the concept that a new LNG-IUS that releases a lower dose of LNG may reduce the incidence of side effects. Furthermore, if the device is smaller than the current one, insertion may be easier and less painful. A difficult or painful procedure may result in failure to insert the device. The two low-dose LNG-IUS use the same T-frame and release 12 µg/day (LNG-IUS12) and 16 µg/day (LNG-IUS16). The main differences are that the current LNG-IUS12 measures 32 × 32 mm and the diameter of the inserter is 4.75 mm, whereas the two new devices measure 28 × 28 mm with an inserter of 3.80 mm in diameter.

The cumulative 3-year Kaplan–Meier analysis for contraceptive failure was 0.005, 0.025 and 0.000 per 100 women/years, while expulsions accounted for 0.4, 2.0 and 1.6% for the LNG-IUS12, LNG-IUS16 and LNG-IUS20, respectively. At the end of the 3-year period, amenorrhea was recorded in 12.7, 18.9 and 23.6% of users of the LNG-IUS12, LNG-IUS16 and LNG-IUS20, respectively. Successful insertions occurred at the first attempt in 98.5% of cases and cervical dilators were used in 9.4% of the LNG-IUS12 group and in 3.9% of the LNG-IUS12/LNG-IUS16 acceptors (p = 0.004). The women reported significantly less pain at insertion with the new devices compared with the current device. This study showed that contraceptive effectiveness with the new smaller LNG-IUS was similar to that found with the device currently on the market.

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