

The new LNG-releasing IUS: a new opportunity to reduce the burden of unintended pregnancy.

Authors:

Ignacio Cristobal^{1,2}, José-Luis Neyro³ and Iñaki Lete^{4,5}

Affiliation:

¹Obstetrics and Gynaecology Department, La Zarzuela Hospital, Madrid (Spain)

²Francisco de Vitoria University, Madrid (Spain)

³Obstetrics and Gynaecology Department, Cruces University Hospital, EHI-UPV, Bilbao (Spain)

⁴Obstetrics and Gynaecology Clinical Management Unit, Araba University Hospital, Araba (Spain)

⁵Vasc Country University, Vitoria (Spain)

Author for correspondence: Ignacio Cristóbal

Address:

Hospital La Zarzuela,

C/ Pleyades 25,

28023 Madrid, Spain

Condensation

Long-acting reversible contraceptive methods (LARC) have been widely recommended to avoid unintended pregnancy at any age. The new intrauterine device Jaydess[®], with the lowest levonorgestrel content and size, is specially suited to address contraceptive needs of young women, especially when considering their nulliparous status.

Abstract

Unintended pregnancies still remain a worldwide public health problem. They have received much attention in adolescents given the strong impact they have on their present and future lives. On the other side, as women join the labour market, young women wishing to delay maternity are also especially vulnerable. Studies have revealed a pattern of use of contraceptive methods that is likely to increase this risk. Methods of long-acting reversible contraception (LARC), among which copper and levonorgestrel-releasing intrauterine devices (IUD and IUS) are the most common, have been widely recommended to avoid unintended pregnancy at any age. Despite this, the use of these devices is very limited. Several barriers to their wide spread use have been identified, which specially affect a higher use by nulliparous women. A new levonorgestrel-releasing IUS containing only 13.5 mg of levonorgestrel (IUS12), recently marketed as Jaydess[®] in Europe, which provides a smaller size, a shorter duration of action, and a lower hormonal content compared to Mirena[®], along with a similar efficacy and safety profile, may offer a long-term option that better addresses the needs of nulliparous women. Evidence on the risk of unintended pregnancies in young women –with a special emphasis in Europe—, barriers associated with a lower-than-desirable use of LARC methods –especially intrauterine devices (IUD and IUS)—, and the potential benefits of the new IUS12 including changes in bleeding pattern, safety and user satisfaction –especially with respect to nulliparous and adolescents— are reviewed here. Evidence supports that IUS12 may offer a LARC option that better addresses the needs of these women.

Key words: Contraception; Contraception behaviour; Contraception, Barrier; Family planning service; Intrauterine devices; unintended pregnancies; levonorgestrel.

Introduction: the burden of unintended pregnancy

Unintended pregnancies persist in today's society as a worldwide public health problem, still affecting 55 out of 1,000 women, despite the reduction observed in the last years concurrent with an increased use of contraceptive methods (1, 2). Estimates in Europe are dramatic, with 44% of the nearly 13.2 million pregnancies taking place among women aged 15–44 years being unintended (1). Besides the health consequences for the mother, unintended pregnancies have social and economic consequences for both, the women and their families (3), and may also have serious consequences on the child (3-6).

Among women at a higher risk of unintended pregnancy, adolescents have received much attention given the strong impact that pregnancies have on their present and future lives (7, 8). Data up to the late 90s reveal that the level of adolescent pregnancy varies by a factor of almost 10 across developed countries, with many Eastern European countries, similarly to the USA, having the highest teen pregnancy rates (70 per 1,000 or more) (9, 10). As a result, in the past decade teenage pregnancy has become a key policy area in several industrialized countries.

In a Pan-European survey conducted in 2006 among 11,490 women aged 15–49 years from 14 European countries (11), optimal mean age for becoming pregnant was relatively high, reaching as much as 27.6 years in Spain. This revealed another vulnerable group that has emerged after women have joined the labour market, i.e. those wishing to delay their first maternity.

Reasons underlying unintended pregnancy

Unintended pregnancies may result from several factors. Once accessibility to contraception

is ensured, cultural, educational, political or socioeconomic issues may affect the use of contraceptive methods. In our setting, where accessibility to contraception is generally easy, still 21–30% of women in the above-mentioned Pan-European study (11) and 23% of women from another study conducted among ~12,000 women from 5 European countries (12), reported using “no method”. However, how many of these women were sexually active remains unknown. Among women using any method in these studies, 18% and 6% respectively reported using unreliable methods of contraception such as cap/diaphragm and natural or withdrawal methods. These studies also revealed that oral contraception was the most widely used method, reaching rates as high as 49% of women in France. Other methods highly dependent on user adherence that require proper use, such as condoms, were also popular, with rates that doubled the average in countries like Spain (39% vs. 17%). This observed pattern of contraception is important since most unintended pregnancies have been shown to result from inconsistent or incorrect use of user-dependent methods, rather than from method failure (13).

Strategies to reduce unintended pregnancies

Besides improving sexual education and accessibility to contraceptive methods, the above-mentioned studies evidence a clear need to increase the use of more effective contraceptive methods. Methods of long-acting reversible contraception (LARC) —these include hormone implants, injectable drugs, copper intrauterine devices (IUDs) and the levonogestrel-releasing system (IUS)—, whose effectiveness is user-independent, have been widely recommended to reduce the rates of unintended pregnancies (14-16) in both older women and adolescents (17). While offering long-term protection, return to fertility is possible as soon as wished, allowing to plan pregnancies. LARC are suitable for a wide range of women, with virtually no contraindications (18). Despite this, these methods are scarcely used by 10% of women in

Europe, with IUDs and the IUS being the most popular ones (8% of all users) (11).

The limited use of LARC has been attributed to several reasons, among them the reluctance of healthcare professionals to offer them to women as a result of inadequate guidance about eligibility and training. Eligibility concerns regarding IUDs and IUS involve especially young women given their nulliparity status (2, 19). These include the belief that uterine insertions are more difficult and complicated, with increased perforation risk and pain, and a higher risk of expulsion and of pelvic inflammatory disease (PID) and subsequent infertility. Other concerns such as the increased risk of ectopic pregnancies or changes in bleeding patterns are not related to parity but still constitute a deterrent for nulliparous women.

Overcoming these barriers by informing and educating healthcare professionals is fundamental (2, 19). However, improvement in contraceptive technology is still needed to better fit the special characteristics of young nulliparous women. No breakthroughs in intrauterine contraception have occurred in the last decade.

A new IUS aiming at meeting special nulliparous needs

A new recently LNG-releasing IUS (IUS12), marketed as Jaydess[®] (except in the USA, marketed as [Skyla[®]]), with a smaller size compared to its predecessor Mirena[®] (IUS20) and a lower LNG content, may offer a LARC option that better addresses the needs of nulliparous women. The new IUS has a 30x28-mm T-shaped polyethylene frame (the smallest in the market) and a reservoir containing 13.5 mg of LNG, a quarter of the content in Mirena[®] (52 mg). Although with an initially *in vitro* daily release rate of LNG of 12 µg, the *in vivo* delivery rate has been shown to be 14 µg/day, decreasing to 10 µg/day in the first 60 days and then gradually over 3 years (licensed period of use) to 5 µg/day (20). Adequate LNG contents of IUS12 and IUS 16 (same-sized IUS containing 19.5 mg of LNG and releasing 16 µg/day)

were tested in a 3-year phase II study where their efficacy and safety were compared to that of IUS20. Although the study was not powered to establish the Pearl Index (number of pregnancies per 100 women-years) or to demonstrate non-inferiority with respect to IUS20, the results showed that the three IUS shared similar efficacy and safety profiles (21). The efficacy of IUS12 was established in a large 3-year phase III, multicentre, randomized, prospective clinical trial, conducted among 2,884 women (39% nulliparous) aged 18–35 years where it was compared to IUS16 (22). The 3-year Pearl Index for IUS12 was 0.33 and 0.31 for IUS16, with no significant differences in pregnancy rates across individual years. This failure rate was as low as that reported for IUS20 at one year (0.2)(23) or at five years (1.1–5.5)(24, 25). The 3-year cumulative failure rate for both IUS was 0.9% and 1.0%, respectively. The contraceptive efficacy was not significantly affected by age, parity status or body weight (26). Moreover, no differences were found between the adjusted and unadjusted Pearl Index, as a result of not needing the women's contribution to method compliance.

Mechanism of action

Similarly to IUS 20 and despite the lower hormone contents, IUS12 mainly exerts its contraceptive effect by thickening the cervical mucus, which impedes the passage of sperm through the cervical canal (20). The high concentration of LNG in the endometrium also down-regulates the endometrial oestrogen and progesterone receptors, leading to a strong antiproliferative effect (20). The high concentration at the uterine cavity is in opposition to the low concentration in serum observed, estimated to be around 162 pg/mL seven days after placement and declining afterwards to reach mean concentrations of 59 pg/mL after 3 years (20). The gradual LNG release is responsible for the relative low and non-fluctuating hormone serum concentration compared to that reached with other hormone methods (27-31) (fig. 1).

In accordance with the minimal LNG systemic exposure, IUS12 has a low impact on ovulation: Ovulation was documented in all IUS12 users in the phase II study during the time periods analysed (21). As with IUS20, with a higher LNG content, fertility is expected to be unaffected after use of the device, with endometrium recovering quickly and normal ovulations being again restored (32). In a European randomized multicentre study, 96% of women in whom IUS20 was removed became pregnant within the first year (33).

Duration of action

IUS12's duration of action is shorter than any other IUD/IUS (3 years), which may address the short- to medium-term maternity wishes of many women. This fact was evidenced in the Pan-European study, where 26% of women using the LNG-IUS reported having used the last IUS for 3–4 years before having it replaced or removed, suggesting that they probably had it removed to have children and then used it again after this break (11, 34).

Easiness of insertion and pain

In the phase III study, placement was successful at the first attempt for $\geq 95\%$ of women, being performed without dilation in most of them ($> 90\%$), regardless of parity (Table 1). Placements were reported as generally easier, and placement-related discomfort was lower in women who had previously had a vaginal delivery than those who had not (nulliparous or women who had had a Caesarean section delivery). In any case, placement was rated as 'easy' in $\geq 84\%$ of nulliparous women (26). As reported with the IUS20 (35), risk of perforation was low, and also regardless of parity, with no complete perforation being reported with any of the two IUS devices tested, and only one partial perforation with IUS16. Crude incidence of total or partial perforation was 0.03% (26).

Pain was rated as 'none' or 'mild' in 41.8% of nulliparous women, in 72,8% of parous women who had had a Caesarean section delivery, and in 81.9% of parous women who had had a vaginal delivery (26). It should be noted that nulliparous women had received local and oral anaesthesia before the procedure in a higher proportion compared to the other women (14.5% vs. 4.5%, and 48.6% vs. 21%, respectively) (Table 1), reflecting the concern of healthcare professionals in this sense (26). The phase II study demonstrated that placements of IUS12 were significantly easier and less painful compared to IUS20, showing also a trend in nulliparous women (21). In view of this evidence, the smaller size of the IUS12 and of the inserter tube may make it suitable for nulliparous women, as well as for those with a smaller uterine cavity, or both (36). As a novelty, IUS12 has a silver ring visible on ultrasound, allowing the confirmation of right placement when needed (32).

Risk of expulsion

The risk of expulsion of the IUS12 in the phase III study was low (although it was higher in the first 12 months) regardless of parity (26). Expulsions were significantly more frequent in parous compared to nulliparous women (4.9 vs. 2.6 cumulative risk at 3 years, respectively). A higher 1-year IUD/IUS expulsion rate in parous vs. nulliparous women has also been observed in the large US-based Contraceptive CHOICE project (37), while others have reported similar expulsion rates at 1 year (38).

Changes in bleeding patterns

This frequent undesirable effect is one of the main causes for IUDs/IUS removal. Irregular bleeding and spotting are common in the first months of IUS use, with a reduction in the number of bleeding or spotting days being observed over time with IUS12, the largest number occurring between the first and second 90-day reference periods (21). More spotting-only days than bleeding days have been reported in all reference periods (21, 22).

Incidence of amenorrhoea is lower with the IUS12 compared to IUS20, occurring in approximately 6% of women during the first year of use, which increases up to 12% after three years (Table 2)(32). A shorter and less frequent bleeding, and a lower tendency to amenorrhoea, was observed with IUS12 vs. IUS16 in the phase III study (39). Discussing bleeding preferences when providing contraception advice is fundamental, as many women may dislike amenorrhoea as they associate it with a loss of fertility and/or femininity or with pregnancy (40). These feelings are highly dependent on cultural and religious backgrounds. For instance, in a study conducted in Finland reduction of bleeding with IUS20 was associated with a higher satisfaction with the method, with amenorrhoeic women reporting satisfaction rates as high as 100% (41).

Satisfaction with bleeding pattern changes with IUS12 has shown to be high, with ~77% of women reporting being 'satisfied' or 'very satisfied', and only ~4.8% of women discontinuing because of bleeding changes (22). A recent randomized, multicentre, phase III profiling study comparing IUS12 with combined oral contraception (COC, 30 µg ethinyl estradiol and 3 mg drospirenone) conducted among 560 women aged 18–29 years (~75% nulliparous) also showed a considerable percentage of IUS12 users who reported being 'very satisfied' or 'somewhat satisfied' with their bleeding pattern (63.1% and 70.0%, respectively) (42). This was so despite the decline over time in the number of bleeding or spotting days experienced, leading to 13.5% of women with amenorrhoea vs. 0.5% of women taking COC after 18 months (43). Irregular bleeding was reported in 21.8% of women using IUS12 and 7.5% of women using COC (43). Another randomized, multicentre, two-arm, open-label phase III study conducted among 759 women aged 18–35 years using either IUS12 or an etonogestrel subdermal implant during 12 months has also reported higher satisfaction rates with IUS12, with almost twice as many women in the IUS12 group as in the etonogestrel implant group

being 'very satisfied' or 'somewhat satisfied' with their bleeding pattern at the end of the study period. At this time, the mean number of bleeding days (excluding spotting) was lower with IUS12, while the percentages of women with amenorrhea and prolonged bleeding were higher with the etonogestrel implant (44).

Safety

Despite the low systemic exposure to LNG with IUS20, progestin-related adverse events are still observed in some users (25). The much lower dose of the IUS12 is expected to reduce these undesirable side effects. In the phase II study, frequency of overall adverse events was in fact lower with IUS12 (66.5% vs. 72.4% with IUS20). Progestin-related adverse events like headache, acne or seborrhoea, which are among the most common with IUS12 (32), showed also a lower frequency compared with IUS20 (21) (Table 3). Ovarian cyst was the only drug-related adverse event that was the most frequently observed in all IUS users in the phase II study, with a great dose-dependent increase of the incidence (5.9% with IUS12 up to 22.0% with IUS20, $P < 0.0001$) (21). This was also confirmed in the phase III study, where the incidence of ovarian cyst was significantly lower with the IUS12 with respect to IUS16 (7.7% vs. 13.8%, respectively) (Table 3)(22). It should be noted that reported cysts included cysts > 3 cm in diameter, regardless of symptoms, which is likely to overestimate the clinical importance of this adverse event. Similarly, given that the presence of progestin-related adverse events was investigated at each visit, their frequency might be higher than when spontaneously reported (21). Removal due to adverse events was only slightly lower with IUS12 than with IUS20 (15% vs. 17%, respectively) (21).

In the phase III study, acne and ovarian cysts were the most frequent adverse events (10.1% and 7.7%). Incidence of acne showed no relation with progestin content (22). Severe adverse

events included perforations and ectopic pregnancies, being reported by 0.6% of women in the IUS12 group and by 1.0% of women in the IUS16 group. During the 3-year period, 21.9% and 19.1% of women respectively, discontinued the use of the device due to any adverse event (22). Adverse event-related discontinuation rates were slightly more frequent among nulliparous women (Table 4). Of the total amount of women in the IUS12 group, 57% completed the study, although the desire to become pregnant before the end of the study was a major reason for discontinuation (26).

The above-mentioned phase III study that compared IUS12 and COC showed that the incidence of drug-related adverse events was higher among IUS12 users (36.6% vs. 15.3% with COC) due to the relatively higher incidence of acne (9.4% vs. 0.4%) and ovarian cyst (5.7% vs. 0.0%). Abdominal pain was also more frequent (5.0 vs. 0.0%). No differences were found in the percentage of women discontinuing the study due to any adverse event (8.9% vs. 8.8%) (43).

Dysmenorrhoea

Dysmenorrhoea improved during the 3-year study period, both in the phase II and in the phase III studies, with no differences among the three IUS (21, 39). In the phase III study, mean days of dysmenorrhoea (any severity) decreased from 14.5 ± 14.1 days at month 1 to 4.3 ± 6.3 days at month 12 (39), being one of the main added values of this new IUS.

Satisfaction

Overall, 95% of women at the phase III study reported being 'very satisfied' or 'somewhat satisfied' with the IUS, with ~80% of them expressing their wish to continue using the device after the study (22). The phase III study comparing IUS12 and COC also reported high

overall satisfaction rates (> 80%) during the 18-month follow-up, with 66.2% of IUS12 users expressing their wish to continue using the device after study completion, compared to 48.8% of women taking COC (42).

Other concerns associated with the use of IUS/IUDs

Among the 2,884 women participating in the phase III study, the percentage of women suffering PID with IUS12 and IUS16 was also low, and even lower among nulliparous women: 0.1% vs. 0.6% in the parous women group ($P = 0.099$). In any case, given the serious consequences of PID, including infertility, patients should be fully evaluated for risk factors associated with PID. OMS eligibility criteria for contraception gives a 'category 1' (no restriction) to the use of LNG-IUS in women with a history of PID if she had a subsequent pregnancy, while a 'category 2' (advantages generally outweigh risks) to women with no subsequent pregnancy or with a current episode of PID (18).

With respect to the risk of ectopic pregnancy, its incidence over the 3-year period was very low, and independent of parity: 0.4% in the nulliparous group, and 0.3% in the parous group ($P = 0.7440$)(22). This rate is lower than that observed in women using no method and similar to that described for other IUDs/IUS (45-47).

IUS12 in adolescents

A single-arm, 12-month phase III study of IUS12 was conducted in 36 centres in eight European countries with the aim of specifically analysing the effectiveness of IUS12 in postmenarcheal adolescents (12–17 years). IUS12 was shown to be highly effective in this population, with no pregnancies taking place during the study period. According to the known bleeding profile of the IUS12, these adolescents generally experienced shorter, less frequent

bleeding and a reduction in dysmenorrhea over time during use. IUS12 was generally well tolerated, with no new or unexpected safety events being associated with its use. IUS12 was associated with high levels of user satisfaction, with more than 80% of women completing the study. Insertions were rated by investigators as 'easy' in 94.4% of cases, and most women (> 50%) reported no more than 'mild' pain during insertion (48).

The importance of information and advice

Lack of awareness of IUD/IUS is also an important barrier to the use of these methods (49-51). In a study where attitude towards IUDs/IUS was analysed, positive attitude significantly increased after a brief educational intervention focusing on benefits and risks, cost-efficacy issues and possible adverse events. Importantly, women were also allowed to physically interact with the device, and a demonstration of how the IUD was inserted and removed was also given (52, 53). The relevance of providing enough information has also been highlighted in another study conducted in Finland among 17,914 IUS users, where information received at the time of insertion strongly correlated with increased user satisfaction (54).

Conclusion

Summarizing, the new IUS Jaydess[®], with a lower LNG content and a smaller size compared to Mirena[®], is associated with easier and less painful placement while keeping a similar efficacy, independently of age or parity. The lower LNG systemic exposure is associated with a lower frequency of overall adverse events including progestin-related events and a lower frequency of amenorrhoea. IUS12 has also shown to significantly reduce dysmenorrhoea. Few women discontinue the use Jaydess[®] due to progestin-related adverse events or changes in bleeding patterns. Other concerns such as the risk of PID or the incidence of ectopic pregnancy are very low. Level of satisfaction is very high, with 95% of women reporting

being 'very satisfied' or 'somewhat satisfied'. Compared to other IUDs/IUS, Jaydess® may be better suited for young women, including nulliparous women. Its 3-year maximum duration of use provides flexibility regarding family planning, while its smaller size may be of benefit when cervical canals are tighter and/or when uterine cavities are smaller.

Table 1. Placement success rates, use of dilation and administration of pain medications by parity status (IUS12 and IUS16 groups combined) (26).

| | Parity status | | |
|--|----------------------------|--|---|
| | Nulliparous (N = 1,130) | Caesarean section only (N = 357) | Previous vaginal delivery (N = 1,397) |
| Placement successful at first attempt, % | 95.0 | 96.1 | 96.9 |
| Placement successful at second attempt*, % | 94.0 (47/50) | 92.3 (12/13) | 97.7 (42/43) |
| Women in whom placement was performed without dilation, % | 90.8 | 93.8 | 97.6 |
| Women who were administered local anaesthesia, % | | | |
| Before the procedure | 14.5 | 5.9 | 4.5 |
| When the procedure proved difficult | 0.5 | 0.0 | < 0.1 |
| When the procedure proved painful | 0.3 | 0.0 | < 0.1 |
| Women who were administered anaesthesia, % | 48.6 | 24.1 | 21.0 |
| Before the procedure | 0.4 | 0.0 | 0.0 |
| When the procedure proved difficult | 4.3 | 0.6 | 1.1 |
| When the procedure proved painful | | | |

*Subgroup who required a second attempt
Data taken from Nelson A. et al. 2012 (26)

Table 2. Frequency of amenorrhoea, and of infrequent, frequent and prolonged bleeding up to 3 years with IUS12 (32).

| | First 90 days | Second 90 days | End of year 1 | End of year 3 |
|---------------------|---------------|----------------|---------------|---------------|
| Amenorrhoea | < 1% | 3% | 6% | 12% |
| Infrequent bleeding | 8% | 19% | 20% | 22% |
| Frequent bleeding | 31% | 12% | 8% | 4% |
| Prolonged bleeding* | 59% | 17% | 9% | 3% |

*Women with prolonged bleeding may have also been included in one of the other categories (excluding amenorrhoea)

Table 3. Summary of adverse events considered to be possibly treatment-related reported by at least 3% of IUS12 users in both, the phase II and phase III studies* and in Mirena[®] users in the phase II study[†] (21, 22).

| Adverse event by MedDRA, n (%) | Phase II study | | Phase III study (N = 1,432) |
|--------------------------------|--------------------|----------------------------------|--------------------------------|
| | IUS12 (N = 239) | Mirena [®] (N = 254) | |
| Progestin-related | | | |
| Headache | 28 (11.7) | 44 (17.3) | 47 (3.9) |
| Nausea | 13 (5.4) | 17 (6.7) | - |
| Altered mood | 34 (14.2) | 25 (9.8) | - |
| Oedema | 10 (4.2) | 17 (6.7) | - |
| Acne | 65 (25.9) | 72 (28.3) | 144 (10.1) |
| Seborrhoea | 16 (6.7) | 20 (7.9) | - |
| Breast pain | 15 (6.3) | 18 (7.1) | - |
| Breast discomfort | 46 (19.2) | 57 (22.4) | |
| Bleeding-related | | | |
| Dysmenorrhoea | 12 (5.0) | 11 (4.3) | 98 (6.8) |
| Vaginal haemorrhage | 9 (3.8) | 4 (1.6) | 65 (4.6) |
| Infections | | | |
| Vulvovaginal candidiasis | 10 (4.2) | 6 (2.4) | - |
| Other | | | |
| Ovarian cyst** | 14 (5.9) | 21 (8.6) | 110 (7.7) |
| Abdominal distention | 33 (13.8) | 4 (1.6) | - |
| Abdominal pain | 13 (5.4) | 14 (5.5) | 48 (3.4) |

MedDRA: Medical Dictionary for Regulatory Activities terminology.

*Or by at least 3% in one of the studies when not reported in the other one.

[†]Differences in adverse events incidence between both IUS12 may be due to differences in reporting.

** Cysts described as abnormal, non-functional, and/or > 3 cm in diameter regardless of the presence or absence of associated symptoms.

Table 4. Completion and discontinuation rates of IUS12 by parity status.

| | Parous (N = 1,754) | Parous (N = 1,754) | P-value |
|--|-----------------------|-----------------------|---------|
| Year 1 completion rate, % | 78.8 | 83.1 | NE |
| Cumulative 3-year completion rate, % | 54.3 | 59.0 | NE |
| Cumulative 3-year completion rate by reason, % | | | |
| Reasons unrelated to adverse events* | 19.6 | 21.7 | 0.3510 |
| Adverse events [†] | 26.1 | 19.2 | 0.0025 |
| Changes in menstrual bleeding pattern [†] | 5.2 | 4.5 | NE |

Adapted from Nelson, A. et al 2012 (26)

NE: not evaluated

*Include withdrawal of consent, protocol deviation, death, lost to follow-up, pregnancy, and “other reasons”

[†]These subjects are a subset of women who discontinued the use of the device “due to adverse events”

Figure 1. Schematic comparison of plasma hormone concentrations for different methods of contraception (27-31).

References

1. Singh S, Sedgh G, Hussain R. Unintended Pregnancy: Worldwide Levels, Trends, and Outcomes. *Stud Fam Plann* 2010; 41(4): 241-50.
2. Lyus R, Lohr P, Prager S, Board of the Society of Family P. Use of the Mirena LNG-IUS and Paragard CuT380A intrauterine devices in nulliparous women. *Contraception* 2010; 81(5): 367-71.
3. Brown S, Eisenberg L. The best intentions: unintended pregnancy and the well-being of children and families. Washington, D.C.: National Academy Press, 1995.
4. Shah PS, Balkhair T, Ohlsson A, Beyene J, Scott F, Frick C. Intention to become pregnant and low birth weight and preterm birth: a systematic review. *Matern Child Health J* 2011; 15(2): 205-16.
5. Cleland K, Peipert JF, Westhoff C, Spear S, Trussell J. Family planning as a cost-saving preventive health service. *N Engl J Med* 2011; 364(18): e37.
6. Myhrman A, Olsen P, Rantakallio P, Laara E. Does the wantedness of a pregnancy predict a child's educational attainment? *Fam Plann Perspect* 1995; 27(3): 116-9.
7. Olausson P, Haglund B, Weitoft GR, Cnattingus S. Teenage childbearing and long-term socioeconomic consequences: a case study in Sweden. *Fam Plann Perspect* 2001; 33(2): 70-4.
8. Kiernan KE. Teenage marriage and marital breakdown: a longitudinal study. *Population Studies* 1986; 40: 34-54.
9. Singh S, Darroch JE. Adolescent Pregnancy and Childbearing: Levels and Trends in Developed Countries. *Fam Plann Perspect* 2000; 32(1): 14-23.
10. Woolf SH, Aron L, eds. US health in International Perspective: Shorter lives, Poorer Health. Washington, D.C.: The International Academics Press, 2013.
11. Cibula D. Women's contraceptive practices and sexual behaviour in Europe. *Eur J Contracept Reprod Health Care* 2008; 13(4): 362-75.
12. Skouby SO. Contraceptive use and behavior in the 21st century: a comprehensive study across five European countries. *Eur J Contracept Reprod Health Care* 2004; 9(2): 57-68.
13. Frost JJ, Darroch JE. Factors associated with contraceptive choice and inconsistent method use, United States, 2004. *Perspect Sex Reprod Health* 2008; 40(2): 94-104.
14. American College of Obstetricians and Gynecologists. Committee on Gynecologic Practice. Long-acting reversible contraception working group. Increasing use of contraceptive implants and intrauterine devices to reduce unintended pregnancy. *Obstet Gynecol* 2009; 114(6): 1434-8.
15. Long-acting Reversible Contraception. The Effective and Appropriate Use of Long-Acting Reversible Contraception. NICE Clinical Guidelines, No. 30. Update 2013: National Collaborating Centre for Women's and Children's Health (UK). RCOG Press, 2005.

16. Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC2009. Available from: <http://www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx>. Date last accessed: November 2014.
17. American College of Obstetricians Gynecologists. ACOG Committee Opinion No. 392, December 2007. Intrauterine device and adolescents. *Obstet Gynecol* 2007; 110(6): 1493-5.
18. Medical eligibility criteria for contraceptive use. Geneva, Switzerland: World Health Organization, 2009. Available from: http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf. Date last accessed: November 2014.
19. Black K, Lotke P, Buhling KJ, Zite NB, Group IcfNwTRiA. A review of barriers and myths preventing the more widespread use of intrauterine contraception in nulliparous women. *Eur J Contracept Reprod Health Care* 2012; 17(5): 340-50.
20. Apter D, Gemzell-Danielsson K, Hauck B, Rosen K, Zurth C. Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies. *Fertil Steril* 2014; 101(6): 1656-62.
21. Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. *Fertil Steril* 2012; 97(3): 616-22.
22. Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. *Obstet Gynecol* 2013; 122(6): 1205-13.
23. Trussell J. Contraceptive failure in the United States. *Contraception* 2011; 83(5): 397-404.
24. Sivin I, el Mahgoub S, McCarthy T, Mishell DR, Jr., Shoupe D, Alvarez F, et al. Long-term contraception with the levonorgestrel 20 mcg/day (LNg 20) and the copper T 380Ag intrauterine devices: a five-year randomized study. *Contraception* 1990; 42(4): 361-78.
25. Andersson K, Odland V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994; 49(1): 56-72.
26. Nelson A, Gemzell-Danielsson K, Drosman SR, Lynen R, Rosen K. A multicenter, randomized, phase 3 study of two low-dose levonorgestrel contraceptive intrauterine systems (LNG-IUS): a subgroup analysis in nulliparous women. Poster P-284 presented at American Society for Reproductive Medicine. October 20 - 24, 2012; San Diego, California. 2012:S196.
27. Wiebe ER, Trouton KJ, Dicus J. Motivation and experience of nulliparous women using intrauterine contraceptive devices. *J Obstet Gynaecol Can* 2010; 32(4): 335-8.
28. Diaz S, Pavez M, Miranda P, Johansson ED, Croxatto HB. Long-term follow-up of women treated with Norplant implants. *Contraception* 1987; 35(6): 551-67.

29. Kuhn W, al-Yacoub G, Fuhrmeister A. Pharmacokinetics of levonorgestrel in 12 women who received a single oral dose of 0.15 mg levonorgestrel and, after a washout phase, the same dose during one treatment cycle. *Contraception* 1992; 46(5): 443-54.
30. Nilsson CG, Lahteenmaki PL, Luukkainen T, Robertson DN. Sustained intrauterine release of levonorgestrel over five years. *Fertil Steril* 1986; 45(6): 805-7.
31. Weiner E, Victor A, Johansson ED. Plasma levels of d-norgestrel after oral administration. *Contraception* 1976; 14(5): 563-70.
32. Jaydess® prescribing information. Available from: <https://www.medicines.org.uk/emc/medicine/28672/SPC/Jaydess+13.5+mg+intrauterine+delivery+system>. Date last accessed: November 2014.
33. Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel-releasing intrauterine device and Nova-T. *Contraception* 1992; 46(6): 575-84.
34. Haimovich S. Profile of long-acting reversible contraception users in Europe. *Eur J Contracept Reprod Health Care* 2009; 14(3): 187-95.
35. Marions L, Lovkvist L, Taube A, Johansson M, Dalvik H, Overlie I. Use of the levonorgestrel releasing-intrauterine system in nulliparous women--a non-interventional study in Sweden. *Eur J Contracept Reprod Health Care* 2011; 16(2): 126-34.
36. Canteiro R, Bahamondes MV, dos Santos Fernandes A, Espejo-Arce X, Marchi NM, Bahamondes L. Length of the endometrial cavity as measured by uterine sounding and ultrasonography in women of different parities. *Contraception* 2010; 81(6): 515-9.
37. Madden T, McNicholas C, Secura G, Allsworth J, Zhao Q, Peipert J. Rates of continuation and expulsion of intrauterine contraception at 12 months in nulliparous and adolescent women. *Contraception* 2010; 82(2): 187-9.
38. Bahamondes MV, Hidalgo MM, Bahamondes L, Monteiro I. Ease of insertion and clinical performance of the levonorgestrel-releasing intrauterine system in nulligravidas. *Contraception* 2011; 84(5): e11-6.
39. Nelson A, Hauck B, Apter D, Rybowski S, Rosen K, Gemzell-Danielsson K. Bleeding Profiles of Two Low-Dose Levonorgestrel-Releasing Intrauterine Systems (LNG-IUSs) Used for Contraception in Nulliparous and Parous Women: Results of a Global, Randomized, Phase III Study. Poster P-277 presented at American Society for Reproductive Medicine. October 20 - 24, 2012; San Diego, California.
40. Salem RM, Setty V, Williamson RT, Schwandt H. When contraceptives change monthly bleeding. *Popul Rep J* 2006; 1(54): 3-19.
41. Heikinheimo O, Inki P, Kunz M, Parmhed S, Anttila AM, Olsson SE, et al. Double-blind, randomized, placebo-controlled study on the effect of misoprostol on ease of consecutive insertion of the levonorgestrel-releasing intrauterine system. *Contraception* 2010; 81(6): 481-6.
42. Buhling KJ, Rybowski S, Roth K, Rosen K. A multicentre, randomised, open-label, Phase III profiling study comparing a low-dose levonorgestrel intrauterine system with

combined oral contraception: analysis of user satisfaction. *Eur J Contracept Reprod Health Care* 2014; 19(1): S74-S5.

43. Buhling KJ, Rybowski S, Roth K, Rosen K. Randomized, multicentre, Phase III profiling study comparing a low-dose levonorgestrel intrauterine system with combined oral contraception: analysis of bleeding, discontinuation rates and adverse events in the 18-months comparative phase. *Eur J Contracept Reprod Health Care* 2014; 19(1): S182.

44. Tuppurainen M, Lukkari-Lax E, Grunert J, Rybowski S. A 12-Month Multicenter, Randomized Phase III Study Comparing a 13.5 mg Levonorgestrel Intrauterine Contraceptive System with the Etonogestrel Subdermal Contraceptive Implant in Women Aged 18–35 Years. Poster presented at the Congress of the American Society for Reproductive Medicine (ASRM), 8-22 October 2014. Honolulu, Hawaii, USA.

45. Sivin I. Dose- and age-dependent ectopic pregnancy risks with intrauterine contraception. *Obstet Gynecol* 1991; 78(2): 291-8.

46. Mirena® Prescribing information. Available from: http://www.mirena.com/html/pdf/Mirena_Prescribing_Information.pdf. Date last accessed: November 2014.

47. Paragard prescribing information Updated 2013. Available from: <http://paragard.com/Pdf/ParaGard-PI.pdf>. Date last accessed: November 2014.

48. Gemzell-Danielsson K, Dermout S, Lukkari-Lax E, Montegriffo E, Rybowski S, Apt D. A Phase III Single-Arm Study of a New 13.5 mg Levonorgestrel Intrauterine Contraceptive System in Postmenarcheal Adolescents: An Evaluation of Efficacy, Bleeding, User Satisfaction, and Placement. Poster presented at the Congress of the American Society for Reproductive Medicine (ASRM), 8-22 October 2014. Honolulu, Hawaii, USA.

49. Allen RH, Bartz D, Grimes DA, Hubacher D, O'Brien P. Interventions for pain with intrauterine device insertion. *Cochrane Database Syst Rev*. 2009(3):CD007373.

50. Hubacher D, Reyes V, Lillo S, Zepeda A, Chen PL, Croxatto H. Pain from copper intrauterine device insertion: randomized trial of prophylactic ibuprofen. *Am J Obstet Gynecol* 2006; 195(5): 1272-7.

51. Rubin SE, Winrob I. Urban female family medicine patients' perceptions about intrauterine contraception. *J Womens Health (Larchmt)* 2010; 19(4): 735-40.

52. Whitaker AK, Johnson LM, Harwood B, Chiappetta L, Creinin MD, Gold MA. Adolescent and young adult women's knowledge of and attitudes toward the intrauterine device. *Contraception* 2008; 78(3): 211-7.

53. Whitaker AK, Terplan M, Gold MA, Johnson LM, Creinin MD, Harwood B. Effect of a brief educational intervention on the attitudes of young women toward the intrauterine device. *J Pediatr Adolesc Gynecol* 2010; 23(2): 116-20.

54. Backman T, Huhtala S, Luoto R, Tuominen J, Rauramo I, Koskenvuo M. Advance information improves user satisfaction with the levonorgestrel intrauterine system. *Obstet Gynecol* 2002; 99(4): 608-13.

