SOCIETY of FAMILY PLANNING
research, education, and leadership

Contraception xx (2010) xxx – xxx

Clinical Guidelines

Use of the Mirena™ LNG-IUS and Paragard™ CuT380A intrauterine devices in nulliparous women

Release date 15 December 2009
SFP Guideline 20092

Abstract

Two intrauterine devices (IUDs) are available in the United States, the levonorgestrel-bearing intrauterine system (Mirena™) and the copper-bearing T380A (Paragard™). These devices have very low typical-use failure rates but are used by only a minority of women. In particular, there is concern about their use in nulliparous women. We review the available data to address common concerns about using IUDs in this population and show that nulliparous women desiring effective contraception should be considered candidates for IUDs.
© 2010 Published by Elsevier Inc.

Keywords: Intrauterine device; Intrauterine contraception; Intrauterine system; IUD; IUS; Nulliparity

Background

Intrauterine devices (IUDs) are highly effective, safe and well-tolerated contraceptives with typical-use failure rates (TUFRs) similar to surgical sterilization [1,2]. Two IUDs are available for use in the United States, the CuT380A, a T-shaped copper-bearing device marketed in the United States as Paragard™, and the T-shaped Mirena™ LNG-IUS (levonorgestrel intrauterine system). Despite their low failure rates, both of these devices remain relatively underused in the United States [3]. According to the 2002 National Survey of Family Growth, only 1.3% of women using contraception reported use of an IUD, while approximately one third use the combined hormonal contraceptive pill, which is significantly less effective for the typical user [1,4].

One reason for this low usage rate is a continued perception among many clinicians that there are strict eligibility criteria that need to be fulfilled for women to use IUDs, such as a history of having had at least one child [5,6]. In a survey of 400 fellows of the American College of Obstetrics and Gynecology, 68% of respondents reported that parity status had a strong affect on their selection of candidates for an IUD [5]. A recently published survey in the United Kingdom found that less than 2% of clinicians said they would recommend an IUD to a 19-year-old nulliparous woman [7]. Particular concerns relate to IUD's effect on the incidence of pelvic inflammatory disease (PID) and infertility, increased complication rates and difficulty with insertion [6–9]. Eligibility criteria for IUD use typically reflected these concerns, which arose from the use of earlier intrauterine contraceptives, such as the Dalkon Shield. When the Paragard™ copper-releasing IUD was first marketed in the United States in 1988, the prescribing information contained a "recommended patient profile," which included a history of childbearing. In 2005, this labeling was amended; the package insert no longer contains language-discouraging use by nulliparous women [10]. However, prescribing information for the Mirena™ LNG-IUS continues to recommend use in women who have had at least one child [11]. In its Medical Eligibility Criteria for Contraceptive Use, the World Health Organization (WHO) designates nulliparity as Category 2 for intrauterine contraception (advantages generally outweigh risks), while for parous women, it is Category 1 (no restriction) [12]. Use of IUDs in nulliparous women is therefore commonly discouraged. Compounding this, many studies of IUDs have excluded nulliparous women, resulting in a limited amount of data to support their use in this specific population. This article will address some of the common concerns raised by use of the Mirena™ LNG-IUS and the Paragard™ IUD in nulliparous women, using data from studies of these and other devices.

Clinical questions and recommendations

1. Does intrauterine contraception maintain its low failure rate in nulliparous women?

Intrauterine devices are highly effective methods of contraception, with TUFRs of 0.2% for the Mirena™

0010-7824/$ – see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.contraception.2010.01.010

LNG-IUS and 0.8% for the Paragard™ CuT380A in the first year of use [1,4]. There are limited data on the failure rates of Mirena™ and Paragard™ stratified by parity. In a prospective study comparing the Mirena™ LNG-IUS with oral contraceptive pills by Suhonen et al. [13], no pregnancies occurred in 94 nulliparous women using the LNG-IUS over 1 year. In another more recent prospective pilot study by Brockmeyer et al. [14], there were no pregnancies among a cohort of nulliparous women using either the LNG-IUS (n=9) or copper-based devices (n=104) at 1 year. A study that evaluated the failure rate of a "frameless" levonorgestrel-releasing IUD designed for nulliparous women also reported no pregnancies in 92 women at 1 year [15]. A study of the Femilis™ IUD (a T-shaped levonorgestrel-releasing device similar to Mirena™) from Belgium included 112 nulliparous women and reported no pregnancies in this group over the 5-year study period [16]. Data from studies of other devices that have been stratified by parity have not shown a difference in failure rate [17,18]. These data suggest that IUDs have a similarly low failure rate in nulliparous and parous women.

2. Is intrauterine contraception acceptable to nulliparous women?

Acceptability of a contraceptive method can be inferred from its continuation rate. Both of the available IUDs have high continuation rates at 1 year [1,4]. In the study of Suhonen et al. [13] comparing the Mirena™ LNG-IUS with oral contraceptive pills, 80% of 94 women using the LNG-IUS chose to continue use after 1 year. In another study comparing LNG-IUS use in nulliparous and parous women, 90% of 92 nulliparous women continued using the method at 1 year [15]. Brockmeyer et al [14] found high continuation rates among 113 nulliparous women using either copper-based devices or the Mirena™ LNG-IUS for 1 year — 65 of 86 women available for follow-up were continuing to use their IUD. Patients in this study also reported high levels of satisfaction with IUDs. While it is easier to discontinue pills than intrauterine contraceptives, continuation rates are a useful surrogate indicator of method acceptability. If continuation rate is considered an accurate reflection of acceptability, IUDs are highly acceptable to women regardless of parity status.

3. Is the rate of expulsion increased in nulliparous women?

The rate of IUD expulsion in parous women, outside the setting of an abortion or delivery, has been reported at 4.2% [19]. A retrospective cohort study of 461 women using IUDs, which included 129 nulliparous women, found no difference in rates of expulsion in nulliparous compared to parous women [20]. One study examining different copper-based devices designed for use by nulliparous women also found no difference in rates of expulsion by parity [21]. Brockmeyer's study reported six expulsions out of 113 women over 1 year, giving an expulsion rate of less than 5% [15]. However, in a review of studies examining the performance of a variety of copper-based IUDs in nulliparous women, Hubacher [21] found that 13 of 20 studies demonstrated an increased expulsion rate in this group. Only one of these studies examined the currently available CuT380A (Paragard™) device. Therefore, while the available data are limited, the expulsion rate for the Mirena™ LNG-IUS appears to be comparable between nulliparous and parous women but may be slightly increased for copper-based devices in nulliparous users compared to parous users.

4. Are side effects increased in nulliparous women?

Common side effects of the CuT380A include increased menstrual bleeding and pain [22]. Levonorgestrel-releasing IUDs have a tendency to lighter, but unpredictable, bleeding and amenorrhea. There are no published studies comparing the side effects experienced by nulliparous and parous users of the Mirena™ LNG-IUS. Hubacher's [21] review investigating copper-based devices found that in 15 of 20 studies, removals for pain and bleeding were slightly increased in nulliparous users compared to parous women. As mentioned previously, only one of these studies looked at the Paragard™ CuT380A specifically, and the increase in removals for bleeding and pain was slight for nulliparous users of this particular device compared with multiparous women.

5. Is the risk of perforation at insertion increased in nulliparous women?

The risk of uterine perforation with insertion of IUDs in all women is between 0% and 1.3% [18]. This risk could theoretically be increased in nulliparous women due to a smaller uterine cavity and greater cervical resistance to dilation. There are no studies directly comparing the rate of perforation at the time of IUD insertion in nulliparous and parous women. In the study of Brockmeyer et al. [14], no perforations were reported during 117 insertions in nulliparous women. One prospective follow-up study did find that increasing parity reduced the risk of perforation with insertion of the CuT380A but included only two nulliparous patients out of a total of 8343 women [23]. It is therefore not possible to make a statement regarding whether or not perforation risk is increased in nulliparous women.

6. Is the risk of PID increased in nulliparous users of intrauterine contraception?

There is no evidence that nulliparous users of IUDs have any greater risk of developing PID than parous users [17]. The Dalkon Shield, an IUD that is no longer available, increased users' risk of PID by a wicking effect of its multifilament string that allowed microbes to ascend into the upper genital tract from the vagina [24]. A large study by the WHO and the Women's Health Study have demonstrated that modern devices, all of which have

monofilament strings, do not increase IUD users' risk for pelvic infection beyond the risk associated with insertion of the device. [25–27]. There appears to be a small transitory increase in the incidence of pelvic infection in the first 20 days after insertion of an IUD in all users [28]. This is likely related to the presence of cervical infection at the time of insertion or the transmission of vaginal bacteria into the uterus. After this period, the risk returns to the background risk for nonusers. In one randomized trial including more than 2500 women, users of the levonorgestrel device had significantly lower rates of pelvic infection than users of a copper-based device; the rate of pelvic infection for users of the copper device was comparable to the rate in nonusers, demonstrating that levonorgestrel IUDs are protective against pelvic infection [29].

7. Are nulliparous users of IUDs at increased risk for developing infertility?

Return to fertility after removal of an IUD is rapid [30], and there is no evidence that this is not the case in nulliparous women. The primary mechanism by which IUDs might increase users' risk for infertility is by the development of PID, leading to pelvic adhesions and tubal disease. As described above, PID is not increased in users of IUDs. A cohort study of 1895 women compared a history of IUD use in three groups: women seeking treatment for primary infertility with tubal occlusion demonstrated on hysterosalpingography, women seeking treatment for primary infertility without tubal occlusion and primigravida pregnant women. The percentage of women reporting prior use of a copper-based IUD was the same in all three groups, suggesting that IUD use does not increase risk for later infertility of either tubal or nontubal etiology. However, later infertility was associated with the presence of anti-*Chlamydia* antibodies [31].

8. Is insertion of intrauterine contraception more difficult or more uncomfortable in nulliparous women?

In nulliparous women, the cervical canal may be narrower than in a parous woman, making the procedure more difficult for the provider and more uncomfortable for the patient. Failed and difficult insertions appear to be increased in nulliparous women compared to parous women [32]. There are few studies directly comparing the discomfort experienced by nulliparous vs. parous women. In a study evaluating whether ibuprofen decreases pain at insertion of the Copper T380A, Hubacher [33] found a statistically significant difference between pain ratings in nulliparous and multiparous women (2.7 and 1.9 on a 10-cm visual analog scale, respectively). However, it is notable that both of these pain scores are low. Misoprostol, a prostaglandin analog and cervical ripening agent, has been studied as a method of facilitating intrauterine access for procedures such as IUD insertion, hysteroscopy and procedural abortion [34]. In one small study of 80 nulliparous women having an IUD placed, misoprostol appeared to aid insertion as judged by the clinician but did not decrease pain or side effects of insertion for the user [35]. Some clinicians provide an oral antiinflammatory drug or apply topical lidocaine preparations to the cervix prior to IUD insertion. While these medications have a low cost and low incidence of side effects, evidence supporting this practice is limited [36].

9. Are nulliparous adolescent women candidates for intrauterine contraception?

The American College of Obstetrics and Gynecology published an opinion article in December 2007 stating that adolescents should be considered candidates for IUDs [37]. Eighty-two percent of teen pregnancies are unplanned, representing one fifth of all unintended pregnancies annually [38]. As a group at high risk for unintended pregnancy, young women desiring effective contraception should be encouraged to consider IUDs. However, further research is required to confirm the acceptability of currently available IUDs in this population [39].

10. Are intrauterine contraceptives designed specifically for nulliparous women superior to standard devices in this population?

Smaller and "frameless" (lacking the horizontal arms) IUDs have been developed specifically to fit more easily inside the smaller uterine cavity of nulliparous women. A large prospective trial of 1170 women in Mexico appeared to show a dramatic difference in the performance of the CuT380A and two copper-based devices designed specifically for nulliparous women [40]. These results are in question, however, due to two factors: first, the study investigators were unblinded; second, the complication and removal rates of the CuT380A were markedly elevated as compared to rates presented in other published research [41]. To date, there is no reliable evidence that devices designed specifically for nulliparous women confer any benefit over the Mirena™ LNG-IUS and the Paragard™ T380A in this population [42].

Conclusion and Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- The Mirena™ LNG-IUS and the Paragard™ T380A are effective and safe contraceptive devices for nulliparous women.
- When compared to other methods of contraception, IUDs have comparable or higher continuation rates of use in nulliparous women.
- IUDs do not increase the risk of pelvic infection or infertility. Levonorgestrel-based devices reduce users' risk of pelvic infection.

ARTICLE IN PRESS

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Due to expulsion rates and bleeding profile, the Mirena™ LNG-IUS may be better tolerated than the Paragard™ CuT380A in nulliparous women.
- Insertion of an IUD may be more challenging in nulliparous women. However, given their benefits, clinicians should not be discouraged from considering them as a first-line contraceptive choice in this group.
- There is currently no credible evidence to support the use of devices designed for nulliparous women over the Mirena™ LNG-IUS and the Paragard™ T380A in this population.

The following recommendation is based primarily on consensus or expert opinion (Level C):

- Adolescent women should be considered candidates for IUDs.

Important questions to be answered

Further research is needed to define the risks and benefits of different IUDs in nulliparous women. Demonstration of the acceptability of IUDs in this population may help to allay clinicians' concerns and increase the use of these highly effective contraceptive methods in this group. Further research into pain control and other methods of easing insertion may be of particular benefit to nulliparous women.

References

[1] Hatcher RA, Trussell J, Nelson A, Cates W, Stewart F, Kowal D. Contraceptive technology 19th edition; 2008.

[2] ACOG Practice Bulletin #59. Obstet Gynecol 2005;105:223.

[3] The Guttmacher Institute. Facts on contraceptive use. Jan 2008. Available at: http://www.guttmacher.org/pubs/fb_contr_use.pdf (Accessed March 2009).

[4] National Survey of Family Growth 2002, Centers for disease control and prevention.

[5] Stanwood NL, Garrett JM, Konrad TR. Obstetrician–gynecologists and the intrauterine device: a survey of attitudes and practice. Obstet Gynecol 2002;99:275–80 [Evidence grade: II-2].

[6] Stubbs E, Schamp A. The evidence is in. Why are IUDs still out? Family physicians' perceptions of risk and indications. Can Fam Physician 2008;54:560–6 [Evidence grade: II-2].

[7] Wellings K, Zhihong Z, Krentel A, Barretta G, Glasier A. Attitudes towards long-acting reversible methods of contraception in general practice in the UK. Contraception 2007;76(3):208–14 [Evidence grade: II-2].

[8] Stanwood NL, Bradley KA. Young women's knowledge of modern intrauterine devices. Obstet Gynecol 2006;108(6):1417–22 [Evidence grade: II-2].

[9] Asker C, Stokes-Lampard H, Beavan J, Wilson S. What is it about intrauterine devices that women find unacceptable? Factors that make women non-users: a qualitative study. J Fam Plan Reprod Health Care 2006;32(2):89–94 [Evidence grade: II-2].

[10] Available online at: http://www.paragard.com/health_care_professional/global/pdf/Prescribing-Info.pdf (Accessed March 2009)

[11] Available online at: http://berlex.bayerhealthcare.com/html/products/pi/Mirena_PI.pdf (Accessed March 2009)

[12] World Health Organization. Medical eligibility criteria for contraceptive use; 2004. updated 2008. Available online at:http://www.who.int/reproductive-health/publications/mec/mec.pdf.

[13] Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. Contraception 2004;69(5):407–12 [Evidence grade: I].

[14] Brockmeyer A, Kishen M, Webb A. Experience of IUD/IUS insertions and clinical performance in nulliparous women — a pilot study. Eur J Contracept Reprod Health Care 2008;13(3):248–54 [Evidence grade: II-2].

[15] Wildemeersch D, Janssens D, Vrijens M, Weyers S. Ease of insertion, contraceptive efficacy and safety of new T-shaped levonorgestrel-releasing intrauterine systems. Contraception 2005;71(6):465–9 [Evidence grade: III].

[16] Wildemeersch D, Janssens D, Andrade A. The Femilis LNG-IUS: contraceptive performance — an interim analysis. Eur J Contracept Reprod Health Care 2009;14(2):103–10 [Evidence grade: III].

[17] Prager S, Darney PD. The levonorgestrel intrauterine system in nulliparous women. Contraception 2007;75(Suppl):S12-5.

[18] Sivin I, Stern J, Coutinho E, et al. Prolonged intrauterine contraception: a seven year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDs. Contraception 1991;44:473–80 Evidence grade: I].

[19] Veldhuis H, Vos A, Lagro-Janssen A. Complications of the intrauterine device in nulliparous and parous women. Eur J Gen Pract 2004;10(3):82–7 [Evidence grade: III].

[20] Dueñas JL, Albert A, Carrasco F. Intrauterine contraception in nulligravid vs parous women. Contraception 1996;53(1):23–4 [Evidence grade: II-3].

[21] Hubacher D. Copper intrauterine device use by nulliparous women: review of side effects. Contraception 2007;75(Suppl):S8–11 [Evidence grade: I].

[22] Rivera R, Chen-Mok M, McMullen S. Analysis of client characteristics that may affect early discontinuation of the TCu-380A IUD. Contraception 1999 Sep;60(3):155–60 [Evidence grade: III].

[23] Caliskan E, Oztürk N, Dilbaz BO, Dilbaz S. Analysis of risk factors associated with uterine perforation by intrauterine devices. Eur J Contracept Reprod Health Care 2003;8(3):150–5 [Evidence grade: III].

[24] Tatum HJ, Schmidt FH, Phillips D, McCarty M, O'Leary WM. The Dalkon Shield controversy. Structural and bacteriological studies of IUD tails. JAMA 1975;231(7):711–7 [Evidence grade: III].

[25] Ebi KL, Piziali RL, Rosenberg M, et al. Evidence against tailstrings increasing the rate of pelvic inflammatory disease among IUD users. Contraception 1996;53:25 [Evidence grade: III].

[26] Lee NC, Rubin GL, Ory HW, Burkman RT. Type of intrauterine device and the risk of pelvic inflammatory disease. Obstet Gynecol 1983;62:1–6 [Evidence grade: III].

[27] Lee NC, Rubin GL, Borucki R. The intrauterine device and pelvic inflammatory disease revisited: new results from the Women's Health Study. Obstet Gynecol 1988;72:1–6 [Evidence grade: II-2].

[28] Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet 1992;339(8796):785–8 [Evidence grade: II-3].

[29] Toivonen J, Luukkainen T, Allonen H. Protective effect of intrauterine release of levonorgestrel on pelvic infection: three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. Obstet Gynecol 1991;77(2):261–4 [Evidence grade: I].

[30] Randic L, Vlasic S, Matrljan I, Waszak CS. Return to fertility after IUD removal for planned pregnancy. Contraception 1985;32(3):253–9 [Evidence grade: III].

[31] Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal

ARTICLE IN PRESS

infertility among nulligravid women. N Engl J Med 2001;345:561 [Evidence grade: II-1].
[32] Farmer M, Webb A. Intrauterine device insertion-related complications: can they be predicted? J Fam Plann Reprod Health Care 2003;29:227–31 [Evidence grade: III].
[33] Hubacher D. Pain from copper intrauterine device insertion: randomized trial of prophylactic ibuprofen. Am J Obstet Gynecol 2006;195:1272–7 [Evidence grade: I].
[34] Fiala C, Gemzell-Danielsson K, Tang OS, von Hertzen H. Cervical priming with misoprostol prior to transcervical procedures. Int J Gynaecol Obstet 2007;99(Suppl 2):68–71 [Evidence grade: II-2].
[35] Sääv I, Aronsson A, Marions L, Stephansson O, Gemzell-Danielsson K. Cervical priming with sublingual misoprostol prior to insertion of an intrauterine device in nulliparous women: a randomized controlled trial. Hum Reprod 2007;22(10):2647–52 [Evidence grade: I].
[36] Allen RH, Bartz D, Grimes DA, Hubacher D, O'Brien P. Interventions for pain with intrauterine device insertion. Cochrane Database Syst Rev 2009(3), doi:10.1002/14651858.CD007373.pub2. Art. No.: CD007373 [Evidence grade: I].
[37] ACOG Committee Opinion No. 392. Intrauterine device and adolescents Obstet Gynecol. 2007; 110(6):1493–5 [Evidence grade: III].
[38] Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. Perspect Sex Reprod Health 2006;38 (2):90–6 [Evidence grade: II-2].
[39] Gold MA, Johnson LM. Intrauterine devices and adolescents. Curr Opin Obstet Gynecol 2008;20(5):464–9 [Evidence grade: III].
[40] Otero-Flores JB, Guerrero-Carreño FJ, Vázquez-Estrada LA. A comparative randomized study of three different IUDs in nulliparous Mexican women. Contraception 2003;67(4):273–6 [Evidence grade: II-2].
[41] Sivin I. Problems in the conduct and analysis of "a comparative randomized study of three different IUDs in nulliparous Mexican women". Contraception 2004;69(3):259–60 [Evidence grade: III].
[42] O'Brien PA, Kulier R, Helmerhorst FM, Usher-Patel M, d'Arcangues C. Copper-containing, framed intrauterine devices for contraception: a systematic review of randomized controlled trials. Contraception 2008;77(5):318–27 [Evidence grade: I].

Sources

PUBMED, MEDLINE and the Cochrane Database were searched for publications related to the use of intrauterine devices in nulliparous and adolescent women. In addition, the references of publications found through these databases were reviewed to capture any additional articles that may have been missed.

Authorship

These guidelines were prepared by Richard Lyus, M.B.B.S., B.Sc.; Patricia Lohr, M.D., M.P.H.; and Sarah Prager, M.D., M.A.S., and were reviewed and approved by the Board of the Society of Family Planning.

Conflict of interest statement

Richard Lyus, M.B.B.S., B.Sc.; Patricia Lohr, M.D., M.P.H.; and Sarah Prager, M.D., M.A.S., report no significant relationships with industries relative to these guidelines. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries.

Intended audience

This guideline is for Society of Family Planning fellows and any other health care professionals involved in the provision of contraception services. It may also be of interest to those involved in sexual and reproductive health education. This evidence-based review should help guide clinicians providing this care, but it is not intended to dictate clinical care.