

# Intrauterine devices and extrauterine pregnancy. A literature review

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## Summary

The incidence of ectopic pregnancy has been high over the last decades. Many risk factors are potential causes, among them IUDs use which might have a significant role. According to the current thinking, the use of IUD does not increase the risk of ectopic pregnancy. However, IUDs are more effective in protecting from intrauterine rather than ectopic pregnancy. Our review focuses on current and past IUD use, duration of its use, type of IUD and the associated risk of ectopic pregnancy. Fertility after IUD removal regarding the incidence of ectopic pregnancy is also discussed. Conflicting results regarding the association of ectopic pregnancy risk with the use of intrauterine devices exist.

**Key words:** Intrauterine devices; Ectopic pregnancy; Fertility; IUD removal; Contraception.

## Introduction

An ectopic pregnancy occurs when the fetus develops outside the uterus. The most common site is the fallopian tube (97.7%) and 80% of these are ampullar [1, 2]. There has been a dramatic increase in the number of ectopic pregnancies over the last decades. The incidence increased from 4.5/1,000 pregnancies in 1970 up to 19.7/1,000 pregnancies in 1992. It should be pointed out that ectopic pregnancy is the major cause of maternal mortality during the first trimester of pregnancy [3, 4]. The main risk factors of ectopic pregnancy are pelvic inflammatory disease (PID), previous ectopic pregnancy, previous tubal surgery, endometriosis, IVF, and in utero diethylstilbestrol exposure [5-9]. Use of an intrauterine device (IUD) as a method of contraception is supposed to be another significant risk factor. Marchbanks *et al.* [5] tried to evaluate the association of ectopic pregnancy with 22 potential risk factors. They found high risk in four possible factors: history of infertility (relative risk - RR: 2.6), history of PID (RR: 3.3), prior tubal surgery (RR: 4.5) and current IUD use (RR: 13.7).

Intrauterine devices are one of the world's most popular methods of reversible birth control. Worldwide, a hundred and six million women use medicated or non-medicated IUDs. Medicated IUDs releasing copper or steroids are used in Europe, North and South America [10], whereas nonmedicated IUDs (single or double steel rings) are widely used in China. It should be mentioned that 30-40% of women in reproductive age in China use IUDs, but only 1-2% of women using contraception in the USA use an IUD [11]. The acceptability of IUD use

in the USA was initially higher but decreased [12] because of the consumer's fear of IUD-related pelvic infection (due to the problems caused by Dalkon Shield IUD) [13, 14]. Most types of IUDs have a plastic T-shaped frame that is wrapped with copper and/or has copper bands. The presence of an IUD in the uterus prompts an inflammatory response by the endometrium and increases the spermicidal effect. Furthermore, an IUD can also change the lining of the uterus preventing implantation. An IUD is usually used for three to five years because it increases the rates of PID (Chlamydia infection, actinomycosis) with longer duration of use. Although, IUD use provides protection against intrauterine pregnancy, many studies have tried to find the association between ectopic pregnancy and IUD use.

## IUDs and ectopic pregnancy

The perception about the role of IUD use in the increase of ectopic pregnancy risk is conflicting. In 1975, Beral *et al.* [15] in their epidemiological study showed that the increasing use of IUDs as a method of contraception may be a significant risk factor the increased ectopic pregnancy rates. Savolainen *et al.* also found a relation between ectopic pregnancy and IUD users [16]. In 1985, a multinational case-control study of ectopic pregnancy organized by the WHO showed an elevated RR (6.4) of ectopic pregnancy when IUD users were compared to pregnant controls [17]. The suggested mechanism of this elevation was that although an IUD provides greater protection against intrauterine pregnancy it predisposes women to PID and tubal damage [17]. Mol *et al.* in 1995 [18] in his meta-analysis showed that current use of an IUD elevates ectopic pregnancy risk whereas oral contraceptives have a protective role [18].

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Parazzini *et al.* in 1995 [19] and Raziel *et al.* in 2004 [20] found a strong relationship between IUDs and ectopic pregnancy. On the contrary, Edelman *et al.* [21] suggested that current and past IUD users do not have an increased risk of ectopic pregnancy and furthermore no relation was found with the longer duration of IUD use [21]. The same results have been shown by numerous authors [12, 22-24]. In 1986, Sandmire *et al.* suggested that former IUD users presented a 2.35% ectopic pregnancy rate and 2.7% remained infertile after IUD removal [25]. Regarding the role of past IUD use, Makinen *et al.* [26] implied that an IUD has a predisposing role in ectopic pregnancy only in users and not in previous users. Furthermore, this was also reported by Randic *et al.* [27] and Xiong *et al.* [28] in their meta-analyses showed that past IUD use mildly increased ectopic pregnancy. The same authors [28] implied that women with current IUD use compared to pregnant controls presented elevated ectopic pregnancy risk, but no correlation was found when compared with non pregnant women.

#### *The role of duration of IUD use*

Many authors tried to investigate the role of duration of IUD use in elevating ectopic pregnancy risk. Ory [29] suggested that IUD users for over 25 months were 2.6 times as likely to have ectopic pregnancy than those with less than 25 months of use and furthermore this difference persisted for one year after the IUD removal. Kalandidi *et al.* [30] showed that past use of IUDs was associated with a RR of 3.89 for ectopic pregnancy and that this RR increased with longer duration of use. Rossing *et al.* [31] found that IUD use for more than three years compared to non-users has a RR of 2.5 and this elevated risk remained for many years after removal. Parazzini *et al.* [19] also found such a correlation. The differences in study design regarding the control group, sample size, and recall bias might possibly contribute to these inconsistencies. Further research is necessary to clarify the association between the risk of ectopic pregnancy and the duration of IUD use.

#### *Ectopic pregnancy risk according to IUD type*

There has been a reduced ectopic pregnancy rate associated with IUD use in recent years [22] due to the use of more effective and safe medicated (copper-containing) IUDs. The currently used copper-containing IUDs have lower failure rates than the nonmedicated IUDs (used in the 1960s and early 1970s) [10, 21]. Many studies indicate that the risk of ectopic pregnancy is higher in Dalkon Shield, Lippes Loop or even TCu-200 users compared to users of other IUD types except the Progestasert IUD [10, 21, 31]. However, there are no statistically significant differences in the risk of ectopic pregnancy between the other types of copper-containing IUDs [10, 21].

Many authors have tried to find out the role of IUD type regarding ectopic pregnancy rates. Ory [29] suggested that the likelihood of ectopic pregnancy was inde-

pendent of the IUD type (copper containing or inert plastic), a finding that Sandmire *et al.* [25] also suggested. However, Chow *et al.* [32] found a very elevated RR (2.5) of ectopic pregnancy in former users of the Dalkon Shield IUD versus other IUD types (RR: 1.7). Sivin *et al.* [10] showed that the less copper an IUD contains, the higher is the incidence of ectopic pregnancy over the time. Sivin *et al.* [10] have estimated that current users of copper IUDs with a surface area of 350 mm<sup>2</sup> have a 91% lower ectopic pregnancy risk than non-users, whereas the risk is even lower when the copper surface is 200 mm<sup>2</sup>. Finally, Ganacharya *et al.* [33] reported that between non-medicated and copper IUDs there was no difference in ectopic pregnancy rates after one year of use but elevated risk in copper IUDs was found after ten years of use.

#### *Fertility response after IUD removal*

Many studies are reassuring for IUD users regarding their future fertility [34, 35]. It has been shown that fertility in women with an IUD in situ [22, 23, 25] or in women with an ectopic pregnancy while using an IUD [6, 17, 23] is excellent, which means that tubal inflammation is immediately reversible after IUD removal, independent of the reason for the removal.

However, many questions have been raised regarding fertility response after IUD removal. Pyorala *et al.* [34] found no statistically significant difference in the return of fertility in women who used either Nova T or Copper T200 IUDs. They also found no significant effect regarding the duration of IUD use and fertility return, and the cumulative probability of pregnancy per 100 women after the IUD removal was 77.3 at one year, 88.9 at two years and 92.4 at three years. Skjeldestad and Bratt [35] found no significant differences in fertility return related to the type of IUD, duration of use, parity or maternal age while checking other IUD types (Nova T, MLCu250 and MLCu375). Sandvei *et al.* [36] after analysing 304 women with ectopic pregnancies also reported that in women with a previous history of ectopic pregnancy, fertility rates are better in IUD users than non-users. Similarly, Wilson *et al.* [37] showed a favourable return of fertility and good pregnancy outcome after IUD removal. In the same study, 91.5% of the nulligravid and 95.7% of the gravid women, respectively, had conceived within 48 months after IUD removal. However, Wilson *et al.* [37] found a difference in ectopic pregnancy rates after IUD removal regarding the reason for removal (0.7% among women who removed the IUD due to complications, e.g., infection vs 0.5% for those that removed it to achieve pregnancy [37]. Furthermore, Andersson *et al.* [38] found that 96% of pregnancies occurred in the first year after IUD removal. In contrast, Bouyer *et al.* [39] showed that the recurrence rate of ectopic pregnancy was higher in women who had had an IUD in place at the time of previous ectopic pregnancy than in those without contraception. Recently, Palladine *et al.* [40] suggested that IUD use less than 3.5 years is not associated with infertility.

On the other hand, Chow *et al.* [32] implied that recent IUD users (< 3 years after removal) still had an elevated risk for ectopic pregnancy. Basuki *et al.* [41] also suggested that discontinuation of IUD use results in a 70% elevation in ectopic pregnancy risk, especially in women with multiple episodes of IUD use and in women with more than three years duration of use. This elevation in ectopic pregnancy risk was also mentioned by Mol *et al.* [18].

#### Ectopic pregnancy rates and contraceptive methods

Franks *et al.* [42] investigated ectopic pregnancy rates among women who used different contraceptive methods. In this study the ectopic pregnancy rate was: 0.005/1,000 women years for oral contraceptives or vasectomy, 0.1/1,000 women years for condoms, 0.15/1,000 women years for diaphragms, 0.318/1,000 women years for tubal sterilisation, 1.02/1,000 women years for IUDs and 2.6/1,000 women years for no contraception. Rossing *et al.* [31] showed that ectopic pregnancy was more likely to occur among IUD users than oral contraceptive users or in women surgically sterilised, but ectopic pregnancy was less likely to occur when compared with non-contraceptive users. Zhang *et al.* [43] in a retrospective study found that according to different contraceptive methods the incidence of ectopic pregnancy varied as follows: 0.18/1,000 women for female sterilisation, 0.21/1,000 women for oral contraceptives, 0.57/1,000 women for condoms or spermicides, 0.65/1000 women for IUD users and 2.43/1,000 women for rhythm or withdrawal method. Basuki *et al.* [41] also found that women develop ectopic pregnancy more frequently without contraception than using contraceptive methods. Finally, Skjeldestad *et al.* [44] in a retrospective analysis showed that relative to non-users of contraception, current IUD users have a 91% protection against ectopic pregnancy, while women with tubal sterilisation had a 60% elevated risk of ectopic pregnancy.

#### Conclusion

Conflicting results regarding the association of the ectopic pregnancy risk with the use of intrauterine devices exist. A pregnancy with an IUD in place is more often ectopic than a pregnancy with no IUD. A slight increase occurs with current IUD use. The role of duration of the use of an IUD to the elevated risk of ectopic pregnancy should be further investigated. Many studies are reassuring for IUD users regarding their future fertility, but further investigations should also be done in this field. Further meta-analyses should be carried out combining the old and the new data regarding the role of IUDs in ectopic pregnancy risk.

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