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Thonneau Patrick, Almont Thierry, La Rochebrochard Elise (de), Maria Bernard, 2006, "Risk factors for IUD failure: results of a large multicentre case-control study", **Human Reproduction**, 21(10), p. 2612-2616. DOI: 10.1093/humrep/del208

Risk factors for IUD failure:

results of a large multicentre case-control study

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Abstract

Objective: This study was conducted to identify the risk factors for intrauterine device failure.

Materials and methods: A retrospective case-control study was carried out between 1999 and 2002. Cases (women with an IUD and a confirmed pregnancy) and controls (women with an IUD who were not pregnant) were recruited by gynaecologists. An anonymous questionnaire was filled in during the consultation, with specific items regarding any type of drugs used before the predicted fertile period for cases and within the cycle which ended in menses for controls.

Results: Two hundred and sixteen cases were compared with 657 controls. Age was associated with intrauterine device failure, with a significantly lower failure risk in women older than 35 years. A significant relationship was observed between a history of IUD expulsion and IUD failure risk (age-adjusted odds ratio 3.31, 95% CI: 1.40-7.81). No relationship was observed between risk of IUD failure and gynaecological background (fibroma, polyps, miscarriage), nor with any type of medicine taken by the woman.

Conclusion: This study is clearly reassuring as we found that anti-inflammatory drugs and any other medicines taken by the woman were not implicated in IUD failure. Only a history of previous IUD expulsion was found to be a risk factor for failure, indicating that these women should have regular medical and echographical follow-up.

Comparing the efficacy rate of various types of IUD, we found a clear advantage for levonorgestrel-releasing devices.

Keywords*:* intrauterine device, intrauterine failure, risk factors, reproductive health, family planning

Introduction

Worldwide, the intrauterine device (IUD) is one of the most frequently used contraceptive methods, and the pregnancy rate of IUD users is estimated at between 1 and 3 per 100 woman-years (WHO, 1990; Mishell, 1998; FFPRHC, 2004a). Although the effectiveness of IUDs is excellent, such failure rates will lead to a substantial number of unwanted pregnancies and subsequent induced abortions. Unfortunately, very few studies have tried to identify the risk factors for IUD failure (Sivin and Schmidt, 1987). In a recent review, several factors (size and shape of the device, technical skills of the healthcare staff, uterine position and length of the endometrium) were analysed but showed no significant relationship with IUD failure. Only the copper content of the device (with a significant link between lowest failure rates and largest copper surface areas) and the age of the woman (reduction of failure rate with increasing female age) were identified as IUD failure risk factors (Thonneau *et al*., 2001). In a case-control study performed in 2003 in Spain (71 cases and 284 controls), the relation between pregnancy in copper-IUD users, uterine position and hysterometry was analysed. Neither of these two gynaecological characteristics was associated with an increased risk of pregnancy (Avecilla-Palau and Moreno, 2003).

More than 15 years ago, a case-control study conducted in France suggested that aspirin use could be a significant risk factor for IUD failure (OR:1.23;1.04-1.46) (Papiernik *et al.*, 1989). Nevertheless, several limitations (absence of a statistically significant relationship with the use of other non-steroidal anti-inflammatory drugs or with steroids) and the low odds ratio observed largely contributed to weaken the authors' hypothesis, which has not as yet been confirmed by other studies.

In order to identify IUD failure risk factors in intrauterine pregnancy, we performed a large case-control study.

Materials and methods

The retrospective case-control study was carried out in France between 1999 and 2002, in close collaboration with the French federation of medical gynaecology and all regional boards of this federation. General information, including the aim and the practical considerations of the study, was delivered by mail and at local meetings to all health professionals involved in family planning. The study was approved by a national ethics board.

Cases and controls were directly recruited by gynaecologists during their own practice. Cases were defined as confirmed pregnancy of less than 4 months duration (positive pregnancy test and/or positive echography) occurring in a woman with an IUD inserted for more than six months, and aged between 18 and 44 years. Controls were the next three following women with an IUD inserted for more than six months, who were not pregnant (last menses within the ten days prior to the consultation) and were aged between 18 and 44 years.

An anonymous questionnaire was administered by the gynaecologist to both cases and controls, and filled in during the consultation. Before the interview, informed consent was given and signed by each volunteer. The items included in the questionnaire were female age, parity and principal reproductive history, type of IUD, number of sexual partners or a new sexual partner (in the last six months), trade name of the IUD. A specific section was also devoted to the medications used by the woman. For cases, we asked about any type of treatment (oral, cutaneous or by injection) taken in the period including the last menses and the following 10 days (i.e. including the predicted fertile period). For controls, we asked women for the same type of information on drugs used during their last cycle (i.e. the cycle which ended in menses). For both cases and controls, if drugs had been used their exact trade name were recorded.

Information collected by gynaecologists was then coded by the research team. Firstly, IUDs were classified by type: levonorgestrel-releasing (LNG-IUD: Mirena®, Schering SA), IUD with copper area between 375 and 380 mm^2 (Gyne T380®, Laboratoire CCD; MLCu375®, Organon; Gynelle 375®, Laboratoire CCD), Cu-IUD with silver core and copper area of 200 mm^2 (Nova T®, Schering SA), Cu-IUD with copper area of 300 mm^2 (Sertalia®, Theramex), and anchored IUD (GyneFix®, Golaz SA).

Secondly, the trade names of drugs taken by the woman were pooled by drug type: steroids and non-steroidal anti-inflammatory agents, antibiotics, analgesics, vaginal antiseptics and anti-depressants. Furthermore, it was determined precisely if the drugs were taken in the 'exposed period', i.e. the last cycle and the following 10 days before the predicted fertile period for cases, and the last cycle for controls.

Statistical analysis

Data were analysed by SAS and Stata software (8.0 versions). The chi-square test was used for comparing percentages. Crude and adjusted odds ratios and 95% confidence intervals were estimated by logistic regression. Sample size, stratifications, adjustments, and other epidemiological analysis were performed according to Schlesselman's recommendations (Schlesselman, 1982). The sample size was calculated to detect a two-fold increase in risk of pregnancy with IUD with a frequency of 5% in controls for alpha = 0.05 and 1-beta=0.80.

Results

During the study period, 1,001 women were enrolled. We excluded 102 women aged 45 years and over. Furthermore, 26 questionnaires were excluded due to lack of key information (age, localisation of the pregnancy for cases). Finally, 216 cases were compared with 657 controls.

Table 1 shows sociodemographic and clinical characteristics of cases and controls. The mean age of cases, 34.3 years (SD = 4.4), was significantly lower than that of controls, 37.0 years (SD = 5.2) ($p<0.001$). Age was associated with intrauterine device failure, with a significantly lower failure risk in women older than 35 years compared with those less than 30-34 years old: OR = 0.49 (95% CI: 0.34-0.71) for age 35-39 years, and OR = 0.14 (95% CI: 0.08-0.23) for age 40-44 years.

No significant differences were observed regarding parity and IUD failure risk, but the number of enrolled women not having given birth was low (n = 28). Educational level, living with male partner**,** size of town of residence, and current IUD past expiry date were not found to be significant IUD failure risk factors.

Table 2 illustrates the distribution of main gynaecological disorders between cases and controls. We observed a significant relationship between a history of IUD expulsion and IUD failure risk (age-adjusted odds ratio 3.31, 95% CI: 1.40-7.81). Similarly, a history of breast disorders was significantly associated with a lower failure risk ($p=0.02$), but this relationship was linked to female age effect (no statistical difference was observed after age adjustment). None of the other variables regarding history of gynaecological disorders were found to be significant risk factors for IUD failure, even after age adjustment.

In this study, 307 women, 82 cases and 225 controls, stated that they had taken medicines within two weeks before conception for cases or in the first part of the last menstrual cycle for

controls. For each case and control, we checked the medicines used and then classified them in types, as anti-inflammatory agents, analgesics, antidepressants, antibiotics, etc.. For drugs classified as anti-inflammatory agents, we analysed steroids and non-steroids separately. Finally and as shown in **Table 3**, none of the medicines taken, of whatever type, were found to be significant risk factors for IUD failure.

We analysed risk of pregnancy according to type of intrauterine device Comparing efficacy between several types of IUD, we found that a levonorgestrel-releasing device (Mirena®) was the most effective. In a regression analysis model (age-adjusted) and taking levonorgestrel-releasing IUDs as the reference group, we found that pregnancy risk was multiplied by 2.70 (95% CI: 1.11-6.56) for IUDs with a copper surface of 375 mm2 (Gyne-T380®, MLCu375®, Gynelle375), by 7.20 (95% CI: 3.01-17.22) for IUDs with a copper surface of 200 mm2 and a silver core (Nova T®), by 8.45 (95% CI, 3.19-22.39) for copper-bearing IUDs with a total copper area of 300 mm^2 (Sertalia®), and by 24.43 (95% CI, 4.73-126.20) for women with the GyneFix® device (however, the number of subjects with this type of IUD was relatively low; n = 9) (**Table 4).**

Discussion

Like previous published studies in this domain (Sivin and Schmidt, 1987; Thonneau *et al.*, 2001), we observed that IUD efficacy is affected by age. In our case-control study, risk of IUD failure was lower in older women, which is due to decreasing fertility with advancing age.

We also observed that a history of IUD expulsion was a significant risk factor for failure of the device (age-adjusted odds ratio 3.31, 95% CI: 1.40-7.81). This item 'history of IUD expulsion' is not mentioned as a significant failure risk factor in the literature. Nevertheless, the consequences of a disproportion between IUD size and the uterine cavity have been analysed by several authors (Anteby *et al.*, 1993; Castro *et al.*, 1993). Hasson *et al.* observed that the length of the endometrial uterine cavity length conditions the effectiveness of IUDs, recording higher rates of pregnancies and expulsion in women where endometrial uterine cavity length was not in adequation with the size of the IUD (Hasson *et al.*, 1976). Furthermore, the intrauterine position of the device, which is closely linked to its contraceptive effectiveness, has been recently assessed in a prospective study of 195 women, where the prevalence of abnormally positioned IUD was as high as 4%, 6 weeks after insertion (de Kroon *et al*., 2003).

We may therefore hypothesize that women with a history of IUD expulsion are likely to have potential unfavourable uterine conditions (small uterine size, slight malformation or malposition), resulting in subsequent devices also being in an abnormal position and so leading to significantly decreased efficacy.

Given that a history of IUD expulsion has to be considered as a risk factor for IUD failure, clinicians involved in family planning must be aware of this information, so that these women may have regular echographical surveillance.

We observed no significant relationship between IUD failure and history of polyps, fibroma, miscarriage or previous pregnancy with IUD (cf. Table 2). These gynaecological backgrounds should not be considered as a formal contraindication for IUD insertion.

In our case-control study, we observed no relationship between use of anti-inflammatory drugs and intrauterine device failure. No significant relationship was observed between any type of medicine taken by the woman and risk of IUD failure. In 1989, French authors found that use of aspirin tablets significantly increased the risk of IUD failure (Papiernik *et al.*, 1989). Nevertheless, their conclusions should certainly be treated with caution due to several limitations. Firstly, in this study medicine use differed significantly between cases (47%) and controls (41%), whereas in our study this variable did not significantly differ between the two groups (p=0.64). Secondly, the difference observed by the above authors in aspirin tablet use was not found with other anti-inflammatory drugs, which is somewhat surprising (in our study, regarding absence of effect of drugs on IUD failure, all drugs had results in the same range). Finally, the very low odds ratio (1.23; 95% CI 1.04-1.46) found by the authors for aspirin tablet use could well be due to a recall bias rather than to a true IUD failure risk effect.

Another interesting finding of this study is that efficacy differed according to the type of IUD. As shown in **Table 4**, levonorgestrel-releasing IUDs were the most effective, which is in agreement with several recent publications (Pakarinen *et al.*, 2003; French *et al.*, 2000; FFPRHC, 2004b). Furthermore, comparison of different types of copper IUDs showed that those with a surface area of less than 300 mm2 were significantly less effective, which is also in accordance with the literature (Batar *et al*., 2002; Cao *et al*., 2004; Cox *et al*., 2002). Risk of pregnancy is known to be higher in women with GyneFix devices (Dennis *et al*., 2001; Wildemeersch *et al*., 2003) but we had relatively few women using this type of IUD (n=9).
Regarding 'history of previous IUD expulsion', the odds ratios were not more significant for LNG-IUDs although the confidence interval was very large (9.3; CI:0.6-134.3), but remained

significant for IUDs with a copper area between 375 and 380 mm^2 (for other types, the number of cases was too small).

Limitations

Due to the retrospective design, recall bias could be an important factor if cases were more likely than controls to remember potential risk factors (medicines taken, for example). In fact, we believe that women are not aware of the potential impact of drugs on IUD effectiveness. Moreover, the proportion of women who had taken any medicines during the study period was very similar, 39% in the case group versus 37% in the control group (p=0.64). Because of this, we may assume that recall bias did not play an important part in our study.

Practitioners taking part in this study did so on a voluntary basis. Although this large multicentre trial involved more than one hundred practitioners, extrapolation of the results to other populations must be done with caution.

Conclusion

Although intrauterine devices are one of the most effective methods of contraception, failures still represent a substantial number of unintended pregnancies. The results of this study are clearly reassuring as we found that anti-inflammatory drugs or any other medicines taken by the woman did not affect IUD efficacy.

In our case-control study, a history of previous IUD expulsion was found to be a risk factor for IUD failure. Nevertheless, a previous expulsion is not a contraindication for a new IUD, on condition that these women have regular medical and echographical follow-up. Finally, comparison of the efficacy rate between various types of IUD showed a clear advantage for levonorgestrel-releasing IUDs, and among Cu-IUDs, for those with the largest total copper area.

Acknowledgments

This research was partially supported by a French PHRC (Public Hospital Programme for Clinical Research) grant, Janssen-Cilag Laboratories, and INSERM (French National Institute of Health and Medical Research).

We thank the French Federation of Medical Gynaecology and all the gynaecologists for their active participation.

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Table 1. Sociodemographic and clinical characteristics of cases and controls

	Cases n (%)	Controls n (%)	Crude OR (95% CI)
Age (years)			
18-24	5 (2.3)	15 (2.3)	0.50 (0.17-1.42)
25-29	28 (13.0)	62 (9.4)	0.67 (0.40-1.13)
30-34	88 (40.7)	131 (19.9)	1 (ref. group)
35-39	75 (34.7)	228 (34.7)	0.49 (0.34-0.71)
40-44	20 (9.3)	221 (33.6)	0.14 (0.08-0.23)
Living with male partner			
No	6 (2.8)	47 (7.1)	1
Yes	209 (97.2)	610 (92.9)	2.68 (1.13-6.37)
Educational level			
Low	124 (58.5)	410 (62.6)	0.84 (0.61-1.15)
High	88 (41.5)	245 (37.4)	1
Size of town of residence			
< 20,000 inhabitants	121 (56.8)	379 (58.8)	0.92 (0.67-1.26)
> 20,000 inhabitants	92 (43.2)	265 (41.2)	1
Parity			
0	5 (2.4)	23 (3.5)	0.66 (0.25-1.76)
1	42 (19.7)	129 (19.7)	0.99 (0.67-1.46)
≥ 2	166 (77.9)	503 (76.8)	1
Current IUD past expiry date			
No	191 (96.9)	616 (97.5)	1
Yes	6 (3.1)	16 (2.5)	1.209 (0.47-3.134)

Table 2. Gynaecological background in cases and controls

	Cases yes/no (%)	**Controls yes/no (%)**	**Crude OR (95% CI)**	**Age-adjusted OR (95% CI)**
History				
uterine-vaginal infection	24/191 (12.5)	93/561 (16.6)	0.76 (0.47-1.22)	
polyps	2/213 (0.9)	8/645 (1.2)	0.76 (0.16-3.59)	
fibroma	5/210 (2.4)	22/630 (3.5)	0.68 (0.26-1.82)	
breast disorders	8/207 (3.9)	57/596 (9.6)	0.40 (0.19-0.86)	0.55 (0.25-1.21)
ectopic pregnancy	1/212 (0.5)	11/644 (1.7)	0.28 (0.04-2.15)	
miscarriage	40/173 (23.1)	115/540 (21.3)	1.09 (0.73-1.62)	
induced abortion	40/173 (23.1)	169/485 (34.8)	0.66 (0.45-0.98)	0.74 (0.49-1.10)
previous pregnancy with IUD	9/180 (5.0)	29/583 (4.5)	1.00 (0.47-2.16)	
IUD expulsion	12/173 (6.9)	14/596 (2.3)	2.95 (1.34-6.50)	3.31 (1.40-7.81)

Table 3. Medicines taken by women before conception (cases) or in the first part of the last menstrual cycle (controls)

	Cases yes/no (%)	**Controls** yes/no (%)	**Crude OR** (95% CI)
Any type of medicine	82/127 (64.6)	225/376 (59.8)	1.08 (0.78-1.49)
Analgesics	18/188 (9.6)	54/544 (9.9)	0.97 (0.55-1.69)
Antibiotics	4/202 (2.0)	10/588 (1.7)	1.16 (0.36-3.75)
Antidepressants	12/194 (6.2)	23/575 (4.0)	1.54 (0.76-3.17)
Anti-inflammatory agents	24/184 (13.0)	60/540 (11.1)	1.17 (0.71-1.94)
- steroids	8/199 (4.0)	12/588 (2.0)	1.97 (0.79-4.89)
- non-steroidal	16/191 (8.4)	50/550 (9.1)	0.92 (0.51-1.66)

Table 4. Efficacy rate according to IUD type (multivariate analysis)

	Cases	Controls	Crude OR (95% CI)	Age-adjusted OR (95% CI)
Levonorgestrel-releasing hormone (Mirena) *	6	87	1 (ref. group)	1 (ref. group)
Cu-IUD copper area 375-380 mm² **	55	293	2.72 (1.13-6.54)	2.70 (1.11-6.56)
Cu-IUD copper area 300 mm² ***	29	40	10.51 (4.04-27.33)	8.45 (3.19-22.39)
Cu-IUD copper area 200 mm² ****	108	218	7.18 (3.04-16.96)	7.20 (3.01-17.22)
GyneFix	5	4	18.12 (3.83-85.68)	24.43 (4.73-126.20)

* Levonorgestrel-releasing IUD (52 mg): Mirena®

** Copper-bearing IUD, total copper area 375-380 mm^2: Gyne T380®, MLCu375®, Gynelle 375®

*** Copper-bearing IUD, total copper area 300 mm²: Sertalia®

**** Copper-bearing IUD with a silver core, total copper area 200 mm^2: NovaT®