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ORIGINAL ARTICLE

'Older' age is a risk factor for pelvic inflammatory disease in intrauterine device users

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Background. To asses the role of a copper intrauterine device (IUD) *per se* in the development of pelvic inflammatory disease (PID) and complicated PID in women considered at low risk of PID.
Methods. Cases were 51 women admitted to hospital with a diagnosis of acute PID, and controls were 50 healthy women attending an outpatient clinic for routine gynecological check-up. The women were 25–45 years old. Data were analyzed and compared between groups using the statistical program package SAS.
Results. IUD use was not associated with an increased risk of PID in general, but in women ≥35 years, IUD use was associated with a risk of PID [odds ratio (OR) = 4.2, confidence interval (CI) 1.1–16.3]. When adjusting for smoking, educational level, employment, and microbial findings in women with PID, IUD use was associated with complicated PID in women ≥35 years (OR = 33.9, CI 1.2–959.6), but not in younger women. When adjusting age and IUD use duration for each other in IUD users, age ≥35 years was a significant risk factor for PID (OR = 4.9, CI 1.3–19.2), but not long (≥5 years) duration. In IUD users with PID, age ≥35 years was a risk factor for a PID to be complicated in both the unadjusted and adjusted analysis (OR = 12.7, CI 1.6–102.3; OR = 12.1, CI 1.4–104.7), whereas long duration of IUD use was not. When adjusting for significant endocervical microbial findings, long duration of IUD use and age, only age ≥35 years, remained significantly associated with both PID and complicated PID (OR = 5, CI 1.1–21.9; OR = 36, CI – 1.9–670).
Conclusions. IUD use was not associated with PID in low-risk younger women, but in women ≥35 years, IUD use was associated with an increased risk of PID. The study also demonstrates an association between IUD use and complicated PID in women ≥35 years.

Key words: intrauterine device; complicated pelvic inflammatory disease

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Pelvic inflammatory disease (PID) affects the upper female genital tract and related structures and may arise from blood-borne infection, such as tuberculosis, or from spread of intra-abdominal inflammation. However, most cases are believed to result from ascending infection from the lower genital tract (1). PID remains one of the commonest causes of morbidity among women and is important economically and socially, because it may lead to serious sequelae, such as persistent pelvic mass, infertility, and chronic pelvic pain (1,2).

The intrauterine device (IUD) has many advantages in terms of effectiveness, ease of use, low cost,

Abbreviations:
PID: pelvic inflammatory disease; IUD: intrauterine device; OR: odds ratio; CI: confidence interval; STI: sexually trans mitted infection.

duration, and reversibility. IUD use varies considerably between regions of the world as well as between the countries in the region or in the country itself (3,4). Ever since the 1920s, when the Gräfenberg ring was introduced, PID has been discussed in relation to IUD use, the main issue being whether IUD *per se* increases a woman's risk of PID (5–7). A second issue is whether the IUD influences the manifestation and clinical course of PID, and if so, how and to what extent (8).

According to a survey in 1997, 20% of women aged 15–45 years in Latvia used IUDs (9). Our study is based on a clinical impression that PID is more frequent in IUD users and, with regard to severity of the disease, more severe in IUD users than in non-users. In order to study a possible association between copper IUD use and PID in the Latvian society with its high IUD acceptance, we designed a case-control study with the following hypotheses: IUD users have a higher risk of PID than non-users, IUD users have different microbiological findings compared with non-users, and IUD users have more severe clinical manifestations of PID than non-users.

The descriptive analysis of the study population will be presented elsewhere. In summary, women with PID (cases) differed significantly from healthy controls by being slightly older (34.8 versus 31.4 years), having shorter education and more often being unemployed and more often smokers. The cases also reported higher total number of induced abortions and longer time since last pregnancy than healthy controls. However, there were no significant differences between cases and controls with regard to typical risk factors for PID such as age at first intercourse, number of lifetime sex partners, duration of current sexual relationship, and number of previous pregnancies and previous episodes of PID. Neither was there any significant difference between cases and controls with regard to contraceptive method use. IUD use was common among both cases (55%) and controls (40%) and this difference was not statistically significant, but IUD users among women with PID had significantly longer duration of IUD use. Regarding microbiology findings, few cases with *Neisseria gonorrhoeae* (one PID case) and *Chlamydia trachomatis* (three healthy cases) were found (10). Combinations of several anaerobic or aerobic microbes were associated with a significantly increased risk of PID and with complicated PID. In IUD users, combinations of several anaerobic/aerobic microbes were associated with an increased risk of PID, irrespective of duration of IUD use (10).

With those results as a background, we decided to study whether IUD use is an independent risk factor for PID, and for a PID to be complicated, in women who are generally considered at low risk of PID, i.e. women older than 25 years and therefore often counseled to use an IUD.

Materials and methods

Study population

Cases were women admitted to hospital with a diagnosis of acute PID, selected according to the following inclusion criteria: age 25–45 years, admitted to hospital for acute PID with the clinical criteria as summarized in Table I. A case was defined as 'complicated PID' if the clinical findings at admission were a palpable adnexal tumor (bilateral or unilateral) at gynecological examination and elevated axillary temperature and at least one of the three of the following laboratory signs: leucocyte count $\geq$10 000/mm^3 or erythrocyte sedimentation rate $\geq$15 mm/hr or C-reactive protein $\geq$20 mg/l. If a woman was an IUD user, the IUD usage had to exceed 1 month in order to avoid directly post-insertion-related complications. Exclusion criteria were pregnancy within the previous 3 months, use of glucocorticoids and antidiabetic drugs, or current use of antibiotics.

Between December, 1998 and January, 2001, all women admitted to Riga 1st Hospital, Dzelzcelnieku Hospital and Lags-Centrs Hospital (Riga, Latvia), who were diagnosed with acute PID according to the protocol criteria, were asked to participate in the study by a duty gynecologist at the clinic. The purpose of the study was presented to every eligible woman orally by a doctor, and before admission to the study, she was asked to sign an informed consent form. In total, 51 sick women were involved in this study as cases. The records of the 51 sick women were reviewed retrospectively, and according to the above-mentioned definition, we constituted two PID outcome groups: an uncomplicated PID case group ($n = 24$) and a complicated PID case group ($n = 27$).

During the same period, women who were healthy and attended outpatient clinics for a routine gynecological check-up without any complaints, in the same age range as the cases, served as controls. Among all healthy consecutive outpatient clinic visitors, 50 women, who met the inclusion and exclusion criteria, were asked to participate as controls by the principal investigator of the study during her work hours.

All participants were asked to complete a structured questionnaire containing 60 questions about their life habits, sexual behavior, and contraceptive use, reproductive and gynecological and medical histories during the hospital stay or outpatient visit. The questionnaire was anonymous, only number-coded, and collected by the principal investigator directly from the woman in a sealed envelope. All participants were informed, orally and in a written form, that their sensitive private information would not be disclosed to anybody. All women underwent a general and gynecological examination.

Table I. Diagnostic criteria for acute pelvic inflammatory disease

1. Lower abdominal pain
2. Abnormal discharge from cervix
3. Adnexal tenderness, cervical and uterine motion tenderness, and palpable mass at gynecological examination
4. At least one of the three of the following laboratory signs:
Leucocyte count $\geq$8000/mm^3
Erythrocyte sedimentation rate $\geq$12 mm/hr
C – Reactive protein $\geq$10 mg/l

Statistical methods and analysis

In the logistic regression analysis, two outcome models were tested: PID outcome, using data from 51 ill and 50 healthy women and complicated PID outcome, using data from 24 uncomplicated and 27 complicated PID cases. Based on significance in the preceding univariate analysis of socio-demographic data and of the analysis of various combinations of the five most frequently detected aerobic and anaerobic microbes in groups, the following variables were selected for testing: education, employment, smoking, and combinations of the aerobic microbes *Staphylococcus* spp. and *Streptococcus* spp. and anaerobes *Bacterioides* spp., *Fusobacteria* spp., and *Peptostreptococcus* spp. IUD use *per se* and the duration of IUD use were selected for analysis for outcome models. As PID women were significantly older than controls and complicated cases were older than uncomplicated PID cases, the influence of age on the development of non-sexually transmitted PID was analyzed. Age groups were dichotomized as below and above 35 years. Long duration of IUD use was defined as $\geq$5 years use of the current copper IUD. All data were analyzed using the SAS statistical package. The results are presented as odds ratios (OR) with 95% confidence interval (CI). A P value <0.05 was considered significant.

Ethics

The Ethical Committee of the Ministry of Welfare of Latvia and Uppsala University approved the study protocol.

Results

Analysis of the whole study group

When the whole study group ($n = 101$) was analyzed for risk factors for PID, using a univariate analysis, IUD use *per se* was not associated with an increased risk of PID in general. However, in the stratified analysis by age groups, IUD use in women $\geq$35 years was associated with a risk of PID (OR = 4.2, CI 1.1–16.3). When adjusting for smoking, educational level, employment, and microbial findings, the association with age $\geq$35 years was still apparent, but became statistically non-significant (Table II). Additionally, unemployment was found to be an independent risk factor for PID regardless of IUD use and age, whereas low educational level was associated with an increased risk of PID regardless of IUD use, but only in women over 35 years (data not shown).

Analysis of PID cases

In order to study factors associated with complicated PID, only PID cases ($n = 51$) were analyzed. The risk of a PID to be complicated was strongly associated with IUD use in the univariate analysis (OR = 8.5, CI 2.4–30.1) as well as in the age group over 35 years (OR = 31.7, CI 2.7–373.3) in the univariate stratified analysis. When adjusting for smoking, educational level, employment, and microbial findings, IUD use remained a very strong independent risk factor for complicated PID (OR = 6.8, CI 1.6–28.5), and after stratifying for age in women $\geq$35 years (OR = 33.9, CI 1.2–959.6), but was not associated with complicated PID in younger women (Table II).

Analysis of IUD user group

In order to study the influence of the duration of IUD use on the risk of PID, only IUD users among cases and controls ($n = 48$) were included in the univariate analysis. IUD use for $\geq$5 years as well as age $\geq$35 years was associated with an increased risk of PID (OR = 5.4, CI 1.5–18.3; OR = 6.8, CI 1.88–24.7). When adjusting age and IUD use duration for each other, age $\geq$35 years remained a significant risk factor for PID in IUD users (OR = 4.9, CI 1.3–19.2) but the association with long duration became non-significant (Table III). In IUD users with PID ($n = 28$), age $\geq$35 years was also a strong risk factor for a PID to be complicated in both the unadjusted and adjusted analysis (OR = 12.7, CI 1.6–102.3; OR = 12.1, CI 1.4–104.7). Long duration of IUD use, however, was not associated with a significantly increased risk of a PID to be complicated in neither analysis (Table III).

When adjusting for duration of IUD use and significant endocervical microbial findings, long duration of IUD use ($\geq$5 years) was associated with a risk of PID (OR = 4.4, CI 1.09–17.6), but was less strongly associated with complicated PID adjusted for microbiology findings (OR = 4, CI 0.6–27.3). When additionally adjusting for age, the effect of IUD use for $\geq$5 years appeared strong, but significance vanished, whereas age $\geq$35 years remained significantly associated with both PID and complicated PID (OR = 5., CI 1.1–21.9; OR = 36, CI – 1.94–670) (Table IV).

Discussion

Few recent studies have collected as many as 51 consecutive hospitalized cases of acute PID for a detailed study of various risk modifiers for the disease. Halperin et al. (2003) (11), in a retrospective study, reported an association between 'older' age and complicated PID. They did not analyze the role of IUD use, although according to their data, 50% of the cases were IUD users. Their data suggested, however, that there was an association between long duration of IUD use and severity of the disease (11). Jamieson et al. (2000) (12), investigating women with PID,

Table II. The risk of having pelvic inflammatory disease (PID) in 50 controls and 51 cases and the risk of having a complicated PID in 24 uncomplicated cases and 27 complicated cases, based on intrauterine device (IUD) use and stratified by age groups in univariate analysis and in multiple regression analysis adjusted for other significant variables

	OR* (univariate)	CI 95%	*P* value†	OR‡ (adjusted)	CI 95%	*P* value†
Healthy/PID case (n = 101)	1.8§	0.8–4.0	0.135	1.7§	0.6–4.6	0.292
25–34 years (*n* = 58)	0.6§	0.2–1.9	0.382	0.6§	0.13–2.4	0.425
≥35 years (*n* = 43)	4.2§¶	1.1–16.3	0.039	3.4§	0.4–28.7	0.262
Uncomplicated case/complicated case (n = 51)	8.5§¶	2.4–30.1	0.0009	6.8§¶	1.7–28.5	0.009
25–34 years (*n* = 23)	1.2§	0.2–8.8	0.858	1.04§	0.1–8.7	0.968
≥35 years (*n* = 28)	31.7§¶	2.7–373.7	0.0061	33.9§¶	1.2–959.6	0.039

OR, odds ratio; CI, confidence interval.
*Univariate analysis OR for variable.
†Wald's test.
‡Multiple logistic regression analysis OR adjusted for significant variables found in univariate analysis: smoking, education, employment, at least two anaerobic microbes in endocervix, and at least three aerobic and anaerobic microbes in endocervix.
§Risk from IUD use.
¶Statistically significant.

reported an association between age ≥35 years and complicated PID. Their study, however, did not analyze IUD users at all. Reljic et al. (1998 and 1999) (13,14) studied laboratory parameters in the management of inpatient cases with severe PID. They did not analyze risk factors for PID in their study population, but according to their data, it appears evident that the average age of the sick women was above 35 years and more than 50% of them were IUD users.

Our findings suggest that long duration of IUD use is important in the development of PID, but as the duration correlates with age, the duration becomes a weaker factor than age in the analysis. Most studies on long usage of IUDs concern contraceptive effectiveness or the finding of *Actinomyces* (15–18). A few studies have reported that long duration of IUD use appears to increase the risk of PID and to complicate its clinical course, but those studies did not further analyze the role of IUD (8,19). Edelman et al. (1990) (19) analyzed risks associated with long-term IUD use in a review article of older studies, and, with regard to the risk of severe PID, stated that some studies show that the risk of complicated PID increase with duration of IUD use.

Our finding that socio-economic factors seem to influence the risk of PID is not easy to explain. Vera et al. (2002) (20) also reported that PID was associated with low socio-economic status rather than presence of typical risk factors for sexually transmitted infection. An apparent potential weakness in our study, as in most other studies on PID, is the choice of control group. Healthy women suitable to serve as controls to women with PID are always difficult to identify, especially in the absence of a population base from which control women could be selected (6,21). However, our controls did not differ from the cases with regard to common risk factors for PID, reproductive history, and contraceptive method use, and they were selected among

Table III. Results of the univariate and multiple logistic regression analyzing only intrauterine device (IUD) users to test the duration of IUD use and age as independent risk factors for development pelvic inflammatory disease (PID) and, among PID cases only, a complicated PID

	OR* (univariate)	CI 95%	*P* value†	OR‡ (adjusted)	CI 95%	*P* value†
Healthy/PID cases (n = 48)						
IUD use 1–5 years versus ≥5 years	5.4§¶	1.5–18.3	0.009	3.7§	0.9–14.5	0.061
25–34 years versus ≥35 years	6.8§¶	1.9–24.7	0.004	4.9**¶	1.3–19.2	0.020
Uncomplicated cases/complicated cases (n = 28)						
IUD use 1–5 years versus ≥5 years	3.3§	0.6–18.6	0.183	3.1§	0.3–23.6	0.282
25–34 years versus ≥35 years	12.7§¶	1.6–102.3	0.017	12.1**¶	1.4–104.7	0.024

OR, odds ratio; CI, confidence interval.
*Univariate analysis OR for variable.
†Wald's test.
‡Multiple logistic regression analysis OR adjusted for both variables.
§Risk from long (≥5 years) duration of IUD use.
¶Statistically significant.
**Risk from older (≥35 years) age.

Table IV. Results of the multiple logistic regression analysis in intrauterine device (IUD) users, adjusting for duration of IUD use, finding of at least two anaerobic microbes or at least three aerobic and anaerobic microbes in endocervix, and age as independent risk factors for the development of pelvic inflammatory disease (PID) and complicated PID

	OR* (adjusted)	CI 95%	*P* value†	OR‡ (adjusted)	CI 95%	*P* value†
Healthy/PID cases (n= 48)						
IUD use 1–5 years versus ≥5 years	4.4§¶	1.1–17.6	0.036	3.0§	0.7–13.5	0.146
At least two anaerobic microbes in endocervix	4.8	0.7–35.3	0.123	4.4	0.5–38.5	0.184
At least three aerobic and anaerobic microbes in endocervix	1.8	0.3–10.6	0.504	2.0	0.3–13.6	0.502
25–34 years versus ≥35 years	NE			5.01**¶	1.1–21.9	0.033
Uncomplicated cases/complicated cases (n= 28)						
IUD use 1–5 years versus ≥5 years	4§	0.6–27.0	0.152	5.9§	0.5–73.7	0.169
At least two anaerobic microbes in endocervix	0.5	0.1–4.9	0.554	0.1	0.008–2.5	0.184
At least three aerobic and anaerobic microbes in endocervix	5.4	0.5–56.0	0.161	24.0	0.9–669.9	0.061
25–34 years versus ≥35 years	NE			36.0**¶	1.9–670.0	0.016

NE, not estimated; OR, odds ratio; CI, confidence interval.
*Multiple logistic regression analysis, OR adjusted for three variables.
†Wald's test.
‡Multiple logistic regression analysis, OR adjusted for all four variables.
§Risk from long (≥5 years) duration of IUD use.
¶Statistically significant.
**Risk from older (≥35 years) age.

women coming to a public routine gynecological health check-up, a habit that is exercised by more than 80% of Latvian women (9). It could be postulated that women with low education or other negative socio-economic factors are less likely to seek early medical care, which might have prevented further progress of the disease, although the cases in the study did not differ from controls in their general health awareness.

The diagnosis of PID in the present study is believed to be accurate, as the inpatient care system in Latvia is strongly controlled by State Insurance Sick Fund system, and due to limited funding, hospitalization of PID patients is only allowed for severe acute PID cases, diagnosed by experienced doctors. In Latvia, confirmation of the clinical diagnosis with laparoscopy is not routinely done. The accuracy and severity of the disease in the present study is demonstrated by the fact that one third of the PID cases subsequently underwent surgery as a part of the treatment, because of the severity of the disease.

Our results show that IUD use *per se* is not associated with PID in women younger than 35 years, whereas non-sexually transmitted PID generally is more severe and complicated in women after 35 years. Those results are in line with other recent studies suggesting that age above 35 years is one factor that predisposes a woman with PID to be complicated (11,12). Moreover, our results suggest that the risk of PID in women over 35 years is even stronger in the presence of an IUD. The study results cannot, however, reasonably explain relationship between older age, IUD use, and the development of PID. We have previously reported that the pathogenesis of PID appears to be associated with a synergistic effect between several pathogens and that this effect probably is facilitated by the presence of an IUD. But the mechanism by which those underlying factors operate and the reason why the association is mainly seen in women over 35 years is poorly understood.

Modern copper IUDs provide very effective contraception, especially for women in the later reproductive period, and are generally recommended for long-term use (4,19,22). Some copper IUDs have been approved for more than 10 years of continuous use (22). Moreover, women in their later reproductive years are often recommended by clinicians to continue using their current IUD until menopause, regardless of IUD labeling. In our study, 18 women were in the age range 40–45 years, of whom 11 were current IUD users. Thus, it seems important to understand the mechanisms behind PID in this age group. Farley et al. (23) in 1992 stated that it is not known whether regular exchange of an IUD would modify the risk, whereas they showed that exchange of an IUD *per se* will increase the risk of insertion-related infection. The mechanism of contraceptive action of modern copper IUDs is still not fully understood, but it is probable that the contraceptive effect depends upon continuous copper ion release, resulting in histochemical changes in the endometrium and endosalpinx, and presence of products of copper wire corrosion in the uterus (24–28). It seems that some of the corrosion products have not only spermicidal and antifertilization effect but also bactericidal effect, particularly at the beginning stages of the corrosion process (29–31). There are scarcely any data in the

literature on corrosion deposit formation of IUDs in relation to possible bacterial infection. It has been suggested that the formation of calcified deposits and incrustments on the device, due to a gradual corrosion process, may have a clinical significance, especially if bacteria are settled on them (32).

In conclusion, we found that IUD use *per se* is not associated with PID in low-risk women younger than 35 years, but that in women 35 years and older, IUD use is associated with an increased risk of PID; further, there is an association between IUD use and complicated PID in women over 35 years, which is possibly influenced by long-term IUD use. Although contraceptive benefits are generally considered to outweigh the risk of PID, we emphasize the need for clinical awareness when monitoring women with IUD use in their later reproductive years.

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