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Intrauterine device use and the risk of pre-eclampsia: a case–control study

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Abstract

Objective—To determine the association between intrauterine device (IUD) use, timing of removal prior to pregnancy, and the risk of pre-eclampsia.

Design—A case–control study within the Clinical Practice Research Datalink, UK.

Setting—Medical record database in the UK.

Sample—Cases of pre-eclampsia ($n = 2744$) were identified among pregnancies resulting in singleton deliveries from 1993 to 2010. Four controls, or pregnancies unaffected by pre-eclampsia, were matched to each case on maternal age, general practice, and year of delivery.

Methods—Data on IUD use were obtained from patient records. The odds ratios (ORs) for the association between IUD and pre-eclampsia were adjusted for covariates identified *a priori*, and analyses were stratified by BMI and number of prior deliveries.

Main outcome measures—Odds ratios (95% confidence intervals, 95% CIs) of pre-eclampsia in pregnancies among women with a history of IUD use, compared with women without a history of IUD use.

Results—Prior IUD use was associated with a reduced risk of pre-eclampsia (OR 0.76; 95% CI 0.58–0.98). The timing of removal in relation to the start of pregnancy showed an inverse association, with shorter intervals associated with a larger decrease in risk of pre-eclampsia. IUD removal within a year prior to pregnancy had an OR of 0.68 (95% CI 0.46–1.00). Among women with a prior delivery, the association between IUD use and pre-eclampsia was null.

Conclusions—Intrauterine device use is associated with a small decreased risk of pre-eclampsia, specifically if removed within the year prior to conception.

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Disclosure of interests

Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

SEP conceptualised and designed the study, performed the analyses, and wrote the article. SSJ designed the study, contributed to the writing of the article, and is responsible for the Boston Collaborative Drug Surveillance Program. MMW designed the study and critically reviewed the article for important content.

Details of ethics approval

Approval for this study was obtained from the Independent Scientific Advisory Committee for the CPRD (protocol 13_127R).

Keywords

Contraception; intrauterine device; pre-eclampsia

Introduction

Studies of contraceptive methods in relation to pre-eclampsia risk have focused on barrier and non-barrier methods, to address hypotheses of cumulative seminal fluid exposure and reduced risks of pre-eclampsia, yet little attention has been given to any specific type of contraception.¹

Intrauterine devices (IUDs) are a method of long-acting reversible contraception and can be copper-containing or hormone releasing. IUD use is common worldwide, with the highest prevalence of usage in several Asian and European countries. Efforts to reduce misconceptions about the risks associated with IUD use in nulliparous women, such as pelvic inflammatory disease and infertility, have contributed to a worldwide increase in their popularity. From 2004 to 2010 the use of hormone-releasing IUDs in the UK increased from 3.1 to 5.2% among women of childbearing age.² Pregnancies conceived with an IUD in place are rare, but have been linked to an increased risk of ectopic pregnancy and spontaneous abortion.^{3,4} Although the effects of an IUD *in situ* on subsequent pregnancy outcomes have been described, the effects of IUD use and removal prior to pregnancy on subsequent pregnancy outcomes have not been well studied.

Copper-containing and hormone-releasing IUDs both alter the cytokine profile of the endometrium, and prevent endometrial proliferation. If the presence of an IUD causes some endometrial damage, it is hypothesised that such injury could improve future implantation and placentation. There is evidence that some level of decidual injury increases the invasion potential of trophoblastic cells to the maternal spiral arteries, a process that when inadequate or incomplete may underlie pre-eclampsia.⁵ The objective of this study was to investigate the association between prior IUD use, timing of removal, and risk of pre-eclampsia using data from the Clinical Practice Research Datalink (CPRD), UK.

Methods

Source population

We conducted a case-control study nested within the CPRD during the period 1993–2010. The CPRD, maintained by the Boston Collaborative Drug Surveillance Program (BCDSP), is a medical record database that was established in 1987 and represents approximately 5% of the population of the UK. The database contains medical record information from general practitioners (GPs), prescription drug data, and referral information. It is estimated that approximately 90% of diagnoses from hospital discharge letters are recorded in the database. Measures to ensure the quality and validity of the data at the BCDSP are in place.⁶

From the CPRD we identified all singleton pregnancies resulting in a live or stillbirth of at least 20 weeks of gestation. We restricted the study population to deliveries with at least 15 months of recorded medical history prior to the delivery date (to allow for the collection of

information on exposure and covariates). The CPRD had 556 739 recorded pregnancies in the period 1993–2010 meeting these criteria.

Case definition

We identified cases of first-time pre-eclampsia in the period 1993–2010 using diagnostic codes in the CPRD. If a woman experienced pre-eclampsia in multiple pregnancies during her follow-up, only the first occurrence was included. Cases included pregnancies affected by pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzyme levels, and low platelet levels), and pre-eclampsia superimposed on pre-existing hypertension. Gestational hypertension and unspecified hypertension during pregnancy were not included as cases. Among the 556 739 eligible pregnancies, 2960 cases of pre-eclampsia were identified.

Control pregnancies were those with no history of pre-eclampsia prior to the index date in the CPRD. Four controls were matched to each case on general practice, year of birth, and maternal age (± 2 years). Women may have contributed more than one control pregnancy ($n = 180$). Cases with no successfully matched controls ($n = 48$) were excluded. Cases and controls with pre-existing chronic hypertension requiring treatment with an antihypertensive were also excluded ($n = 158$).

Intrauterine device use

Intrauterine device (IUD) use prior to the start of pregnancy was determined using procedure codes, drug codes, and record review. Procedure codes, indicating IUD insertion, removal, follow-up, or complications, and drug codes, indicating the receipt of an IUD at any point from the start of the patient record through to the date of delivery, were used to identify subjects using an IUD. IUD use was defined as any IUD receipt prior to the index pregnancy without an intervening pregnancy.

The interval between IUD removal and the start of pregnancy was calculated by subtracting the date of IUD removal from the pregnancy start date. The pregnancy start date was defined as the date of the last menstrual period (LMP). Approximately half of all deliveries in the CPRD have a recorded LMP date. For deliveries that did not have an LMP date, but had an estimated date of delivery (EDD), the start date of pregnancy was calculated by subtracting 280 days from the EDD. The start date of pregnancy for pregnancies without an LMP or EDD (51.6%) was estimated by subtracting 280 days from the date of delivery. If an IUD removal date was not recorded, the last recorded date of an IUD procedure code was used to calculate the timing of removal. Subjects with an IUD procedure code after the start date of pregnancy were categorised as having an IUD *in situ* at the start of pregnancy. The timing of removal was categorised as *in situ*, <12 months, and ≥ 12 months.

Covariates

Information on body mass index (BMI) and smoking prior to the start date of pregnancy was collected. BMI (kg/m^2) was categorised as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), or obese ($\geq 30 \text{ kg/m}^2$). Smoking was categorised as ever or never. Data on pre-existing diabetes, fertility problems and treatment,

and induced abortions prior to the start date of the study pregnancy were collected. Parity information is not available for each pregnancy in the CPRD, but was estimated by identifying the number of deliveries resulting in a stillbirth or live birth prior to the study pregnancy, and categorised as 0 or 1.

Statistical analysis

The distributions of demographic and reproductive characteristics were calculated for cases and controls. IUD use was examined as a dichotomous variable: any use versus no use. Among IUD users, the timing of removal in relation to the pregnancy start date was also examined. Conditional logistic regression models, accounting for the matched study design, were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs), which were in turn used as estimates of risk ratios. Unconditional logistic regression models yielded similar results, indicating no confounding by the matched variables, therefore unconditional models were used in sub-analyses to improve precision. Confounding factors were identified *a priori* based on associations with both IUD use and pre-eclampsia, and included pre-pregnancy BMI, smoking, history of diabetes, fertility problems, or induced abortion. BMI and smoking information were missing for approximately 25 and 15% of subjects, respectively. Multiple imputation methods using ten imputed data sets were used to impute missing information on BMI and smoking. Variables used to impute missing data included maternal age, birth year, prior deliveries, induced abortion, hypertension, diabetes, fertility problems, infertility treatment, pre-eclampsia, and IUD use.

Nulliparity, or no prior deliveries, is an established risk factor for pre-eclampsia. Additionally, nulliparous women are less likely to use an IUD as a method of contraception.⁷ Data on parity is unavailable in the CPRD, but the number of prior deliveries recorded for a woman can be tallied. As a result of the potential for parity to confound the relationship between IUD use and pre-eclampsia, the impact of confounding was assessed in several ways. Multiple imputation methods, described above, were used to impute parity. Women with prior recorded deliveries could accurately be classified as parous (nulliparity = 0), whereas women without a prior delivery may have been nulliparous or may have had a prior delivery unrecorded in the CPRD. Among this latter group, women that had a record beginning in adolescence without a recorded delivery were considered nulliparous (nulliparity = 1); parity for all remaining women was imputed.

A stratified analysis to assess effect measure modification by prior deliveries was performed among all women, and then among women with a minimum of 10 years of active follow-up, allowing for more complete information on prior deliveries. Effect measure modification by pre-pregnancy BMI was also assessed by stratifying $<25 \text{ kg/m}^2$ or $\geq 25 \text{ kg/m}^2$, and then comparing differences in measures of association. Women with a missing BMI measurement were excluded from this stratified analysis.

Several sensitivity analyses were also performed. To address the potential for misclassification of timing of IUD removal in relation to the pregnancy start date, we restricted the analysis to those with a recorded LMP and an exact IUD removal date. Additionally, to address concerns about differences between women seeking contraceptive care from family planning clinics, which would not be captured in the CPRD, and women

using their GPs to obtain contraception, an analysis restricted to women with a GP-recorded contraceptive-related visit or prescription in the 3 years prior to the pregnancy start date was conducted. Contraceptive-related codes included those relating to oral contraceptive pills, injectable contraceptives, subcutaneous contraceptive implants, or patches, diaphragms, spermicides, and cervical caps. A similar sensitivity analysis restricted to women using non-barrier methods of contraception was also conducted.

Results

There were a total of 2744 pre-eclampsia cases and 11 156 controls included in this analysis. Compared with controls, cases were more likely to be overweight (22.7 versus 19.5%) and obese (17.0 versus 10.6%). Pre-pregnancy BMI measurements were recorded on average 2.3 years prior to the pregnancy start date, with approximately 45% of subjects having a measurement within 2 years of the pregnancy start date. Restricting data on BMI to those with a measurement recorded within 2 years prior to pregnancy did not change the distributions. Cases were less likely to ever have smoked and less likely to have had a prior delivery. Pre-existing diabetes was more common in cases. Among controls, IUD users were more likely to be older, overweight or obese, have at least one prior delivery, and a history of induced abortion, than non-IUD users (Table 1).

The use of an IUD prior to pregnancy was slightly less common among cases compared with controls (3.0 compared with 4.4%). The adjusted OR for the association between IUD use and pre-eclampsia was 0.85 (95% CI 0.66–1.10). Adjustment for imputed parity instead of prior deliveries resulted in a decreased point estimate of 0.76 (95% CI 0.58–0.98). The association differed by timing of removal, with odds ratios of 0.68 (95% CI 0.46–1.00) among women having an IUD <12 months prior to pregnancy and 0.86 (95% CI 0.60–1.22) among women with an IUD 12 months before pregnancy (Table 2).

Among women with recorded BMI information, IUD use was similarly associated with a reduced risk of pre-eclampsia among women with a BMI < 25 kg/m² (OR 0.67, 95% CI 0.43–1.04), compared with women of BMI ≥ 25 kg/m² (OR 0.77, 95% CI 0.54–1.10) (Table 3).

Effect measure modification by any prior deliveries recorded in the CPRD was assessed. The adjusted OR for IUD use and pre-eclampsia was 0.64 (95% CI 0.44–0.93) among women with no prior deliveries recorded in the CPRD, whereas the association among parous women was null. Approximately 22% of cases and 20% of controls had 10 years or more of recorded information in the CPRD prior to the study pregnancy. Analyses restricted to those with ≥ 10 years of follow-up, allowing for improved ascertainment of prior deliveries, similarly showed a nearly null association between IUD use and the risk of pre-eclampsia among women with at least one prior delivery. The 95% confidence intervals for the results of the stratified analyses were wide, and demonstrated considerable overlap between strata (Table 4).

To address the potential for misclassification of the timing of IUD removal, analyses restricted to women with a recorded LMP and a recorded IUD removal date were performed.

Among those with an IUD, 30% of cases and 32% of controls had a recorded LMP and a recorded removal date. The association between any IUD use and pre-eclampsia was similar to the effect found in the primary analysis. The results for timing of removal were also comparable with the primary analysis, with adjusted ORs of 0.53 (95% CI 0.12–2.34) for *in situ*, 0.67 (95% CI 0.38–1.18) for <12 months, and 0.85 (95% CI 0.40–1.80) for 12 months. The 95% confidence intervals for these estimates were imprecise, and included the null value.

Nearly 70% of both cases and controls had a record of contraceptive use within 3 years of the study pregnancy. Among women consulting with their GP for contraceptives, IUD use was associated with a reduced risk of pre-eclampsia (OR 0.63, 95% CI 0.48–0.83). Upon restricting the analysis to women using non-barrier methods of contraception, the odds ratio between IUD use and pre-eclampsia was 0.69 (95% CI 0.52–0.92).

Discussion

Main findings

The use of an IUD prior to pregnancy was associated with a small decrease in the risk of pre-eclampsia among women with an IUD *in situ* and women using an IUD within 1 year of the study pregnancy. There was no association between IUD use and pre-eclampsia among parous women.

Strengths and limitations

From 1993 to 2010 the CPRD contained records for over half a million pregnancies that met the inclusion criteria of the present study. In the UK, health care coverage is universal, and general practitioners play an integral role in maternity care: pre-conception, antenatal, and postpartum.⁸ Therefore, pregnancies included in the CPRD were not selected based on type of service utilisation. Information in the CPRD is recorded by trained GPs, thereby eliminating a reliance on self-reported information on exposure, outcome, and covariates. Despite the large sample of pregnancies available for analysis in the CPRD, both IUD use and pre-eclampsia were uncommon, resulting in imprecise estimates for the majority of associations presented in this analysis.

A limitation of this study is incomplete information on parity. Several analyses were performed to address the potential impact of confounding by parity on our findings. Adjustment for prior deliveries recorded in the database, used as a proxy for parity, attenuated our findings, but point estimates for IUD use *in situ* and <12 months prior to pregnancy indicated a 25% (OR 0.75, 95% CI 0.31–1.80) and 17% (OR 0.83, 95% CI 0.56–1.22) reduction in risk of pre-eclampsia, respectively. Using this proxy is likely to overestimate the prevalence of nulliparity, given the potential for women to have had a prior delivery that was not captured by the CPRD, and therefore the attenuation of the odds ratio towards the null value (OR 0.86) would have been exaggerated. Approximately 49% of control pregnancies in the CPRD were to women with no recorded prior delivery. Birth statistics from the UK in 2007 reported that the proportion of deliveries to nulliparous married women is 43%, providing evidence that the CPRD slightly overestimated

nulliparity.⁹ Multiple imputation methods were also used to impute and adjust for parity, similarly resulting in an attenuated but still protective effect of IUD use on pre-eclampsia (OR 0.77). Lastly, the results of a quantitative bias analysis for an unmeasured confounding factor demonstrated that under several plausible scenarios of the prevalence of nulliparity among IUD users and non-users, the association between IUD use and pre-eclampsia was attenuated, but not completely accounted for by adjustment for parity. Effect measure modification by parity was also assessed. Among women with at least one prior delivery, there was no association between IUD use and risk of pre-eclampsia. The lack of information on partner change is also a limitation. Partner change is negatively associated with IUD use and positively associated with pre-eclampsia; therefore, adjustment for partner change could potentially attenuate the observed odds ratios from the present study.

Incomplete and inaccurate recording of dates in the CPRD should also be noted as a limitation. An LMP date was recorded for approximately half of the pregnancies included. Sensitivity analyses restricted to women with the most accurate dates for pregnancy and IUD use strengthened our results, indicating that the misclassification of timing of removal attenuated our results. The results of this sensitivity analysis were based on a small number of exposed cases with complete dates, and therefore 95% confidence intervals were wide and included the null value.

The prevalence of pre-eclampsia among singleton pregnancies in the CPRD from 1993 to 2010 was 0.5%, which is less than the estimated 4% among nulliparous women and 1.7% among parous women from a Swedish study,¹⁰ and the overall prevalence of 3.8% in the USA.¹¹ A review of validation studies of diagnoses in the CPRD reported a median positive predictive value of 89% across 183 diagnoses.¹² Although reproductive and perinatal diagnoses were not included, hospital discharge registers report positive predictive values of 71–74% and specificities of >99% for diagnoses of pre-eclampsia.^{13,14} Although the under-ascertainment of pre-eclampsia cases is a limitation, the specificity is expected to be high, thereby reducing the number of false positives. Additionally, any true pre-eclampsia cases that were misclassified and included as controls would represent a small proportion of all selected controls.

Interpretation

To our knowledge this is the first study to investigate IUD usage and timing of removal prior to pregnancy in relation to risk of pre-eclampsia. Studies of IUDs *in situ* in relation to risk of pre-eclampsia have previously been published. In the present study we report a reduction in the risk of pre-eclampsia for women with an IUD *in situ* (OR 0.53, 95% CI 0.12–2.34), although our finding is based on just two exposed cases with recorded information on both IUD removal and LMP. Despite small numbers, this finding is consistent with a study performed in a cohort of South American women that reported a 40% decreased risk of pre-eclampsia among women with an IUD *in situ* at the time of conception.¹⁵ Another study reported a lower frequency of mild and severe pre-eclampsia among women conceiving with an IUD in place than among those without an IUD,¹⁶ although no measures of association were calculated. Although we report a reduced risk of pre-eclampsia, it is important to note that an IUD retained during pregnancy is associated with several adverse obstetric outcomes,

and a plan to safely remove the device early in pregnancy should be implemented. The mechanism through which IUD use reduces the risk of pre-eclampsia may be through a process involving endometrial injury. IUD use causes some level of mechanical injury to the endometrium, as evidenced by a chronic inflammatory response to copper IUDs and an altered cytokine profile to both copper and hormonal IUDs. Endometrial injury has been demonstrated to improve implantation and subsequent placentation among populations undergoing assisted reproductive technologies.¹⁷ The observed null associations between IUD use more than 1 year before the study pregnancy may indicate that any effect of IUD use on pre-eclampsia wanes over time. The effects of IUD use on the endometrium may differ by type of IUD, and subsequently may have different implications on pre-eclampsia risk.¹⁸ As a result of the limitations of the present study we were unable to assess whether associations with pre-eclampsia differed by IUD type.

The prevalence of IUD use among controls was 4.4% from 1993 to 2010, which is similar to the contraceptive prevalence in the UK of 4–6% reported from 1993 to 1995, but less than that of 10–11% reported from 2007 to 2009,¹⁹ indicating an increase in IUD usage. In addition to a patient's general practice, contraceptives can be obtained through family planning clinics in the UK. The use of family planning clinics in the UK has been declining. In 2010, approximately 10% of women in the UK used clinics for their contraceptive method.²⁰ Although women may have used clinics for IUD procedures, restricting the analysis to women with GP-recorded contraceptive information did not alter the study results.

Conclusion

The use of an IUD prior to pregnancy was associated with a small reduction in the risk of pre-eclampsia. The recency of removal impacted the findings, indicating that the timing of IUD use in relation to pregnancy may offer insight into the etiology of pre-eclampsia. As a result of the small number of IUD users and incomplete data on confounding factors in the present study, future studies are needed to provide a better understanding of the association between IUD use, particularly the timing of removal and type, and pre-eclampsia.

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Table 1

Characteristics of pre-eclampsia cases and controls and IUD users and non-users among controls in the Clinical Practice Research Datalink, 1993–2010

	Cases (<i>n</i> = 2744)				Controls			
	All controls (<i>n</i> = 11 156)		IUD use (<i>n</i> = 487)		No IUD use (<i>n</i> = 10 669)			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Body mass index (kg/m²)								
Underweight (<18.5)	56	2.0	355	3.2	8	1.6	347	3.3
Normal (18.5–24.9)	939	34.2	4648	41.7	194	39.8	4454	41.7
Overweight (25–29.9)	624	22.7	2175	19.5	110	22.6	2065	19.4
Obese (≥ 30)	466	17.0	1177	10.6	70	14.4	1107	10.4
Missing	659	24.0	2801	25.1	105	21.6	2696	25.3
Smoker								
Ever	892	32.5	4124	37.0	215	44.1	3909	36.6
Never	1453	53.0	5399	48.4	221	45.4	5118	48.0
Missing	399	14.5	1693	15.2	51	10.5	1642	15.4
Prior deliveries in CPRD[*]								
0	1991	72.6	5416	48.5	139	28.5	5277	49.5
1	753	27.4	5740	51.5	348	71.5	5392	50.5
Prior induced abortion	363	13.2	1722	15.4	131	26.9	1591	14.9
Pre-existing diabetes	44	1.6	57	0.5	4	0.8	53	0.5
Fertility problems	317	11.6	1124	10.1	36	7.4	1088	10.2
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Maternal age (years)	28.9	6.1	29.1	5.8	30.9	4.9	29	5.8

^{*} Number of prior deliveries (still birth or live birth) recorded in the CPRD.

Table 2

Odds ratios and 95% confidence intervals for the association between IUD use, timing of removal, and pre-eclampsia; CPRD, 1993–2010

	Cases (n = 2744) n (%)	Controls (n = 11 156) n (%)	Unconditional OR (95% CI)	Conditional ORs (95% CIs) for pre-eclampsia	
				Unadjusted	Adjusted*
IUD use					Adjusted**
Yes	83 (3.0)	487 (4.4)	0.68 (0.54–0.87)	0.69 (0.54–0.88)	0.85 (0.66–1.10) 0.76 (0.58–0.98)
No	2661 (97.0)	10669 (95.6)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Timing of removal					
<i>In situ</i>	6 (0.2)	45 (0.4)	0.54 (0.23–1.25)	0.52 (0.22–1.22)	0.75 (0.31–1.80) 0.62 (0.26–1.48)
<12 months	34 (1.2)	237 (2.1)	0.58 (0.40–0.83)	0.60 (0.41–0.86)	0.83 (0.56, 1.22) 0.68 (0.46–1.00)
12 months	43 (1.6)	205 (1.8)	0.84 (0.60–1.17)	0.84 (0.60–1.17)	0.89 (0.63–1.26) 0.86 (0.60–1.22)

* Adjusted for BMI (with imputation), smoker (with imputation), prior deliveries, induced abortion, fertility problems, and pre-existing diabetes.

** Adjusted for BMI (with imputation), smoker (with imputation), parity (with imputation), induced abortion, fertility problems, and pre-existing diabetes.

Table 3

Odds ratios and 95% confidence intervals for the association between IUD use, timing of removal, and pre-eclampsia, stratified by BMI, 1993–2010

	Underweight/normal (BMI < 25 kg/m ²)			Overweight/obese (BMI ≥ 25 kg/m ²)		
	Cases (<i>n</i> = 995) <i>n</i> (%)	Controls (<i>n</i> = 5003) <i>n</i> (%)	Adjusted OR* (95% CI)	Cases (<i>n</i> = 1090) <i>n</i> (%)	Controls (<i>n</i> = 3352) <i>n</i> (%)	Adjusted OR* (95% CI)
IUD use						
IUD	24 (2.4)	202 (4.0)	0.67 (0.43–1.04)	41 (3.8)	180 (5.4)	0.77 (0.54–1.10)
No IUD	971 (97.6)	4801 (95.9)	1.00 (ref.)	1049 (96.2)	3172 (94.6)	1.00 (ref.)
Timing of removal						
<i>In situ</i>	2 (0.2)	19 (0.4)	0.65 (0.15–2.87)	3 (0.3)	20 (0.6)	0.55 (0.16–1.91)
<12 months	10 (1.0)	95 (1.9)	0.64 (0.33–1.24)	16 (1.5)	92 (2.7)	0.61 (0.35–1.06)
12 months	12 (1.2)	88 (1.8)	0.71 (0.37–1.32)	22 (2.0)	68 (2.0)	1.02 (0.62–1.70)

* Unconditional logistic regression adjusted for maternal age, birth year, smoker (with imputation), parity (with imputation), induced abortion, fertility problems, and pre-existing diabetes.

Table 4

Odds ratios and 95% confidence intervals for the association between IUD use and pre-eclampsia, stratified by prior deliveries in the CPRD

	Cases <i>n</i> = 2744 <i>n</i> (%)	Controls <i>n</i> = 11 156 <i>n</i> (%)	OR (95% CI) for pre-eclampsia	
			Unadjusted	Adjusted [*]
No prior delivery				
IUD	35 (1.3)	139 (1.3)	0.68 (0.47–0.99)	0.64 (0.44–0.93)
No IUD	1956 (71.3)	5277 (47.3)	1.00 (ref.)	1.00 (ref.)
1 prior delivery				
IUD	48 (1.8)	348 (3.1)	1.06 (0.77–1.44)	1.03 (0.75–1.42)
No IUD	705 (25.7)	5392 (48.3)	1.00 (ref.)	1.00 (ref.)
Subjects with 10 years of follow-up				
	Cases <i>n</i> = 590 <i>n</i> (%)	Controls <i>n</i> = 2210 <i>n</i> (%)	OR (95% CI) for pre-eclampsia	
			Unadjusted	Adjusted [*]
No prior delivery				
IUD	8 (1.4)	33 (1.5)	0.61 (0.28–1.32)	0.56 (0.25–0.99)
No IUD	401 (68.0)	1002 (45.1)	1.00 (ref.)	1.00 (ref.)
1 prior delivery				
IUD	10 (1.7)	78 (3.5)	0.83 (0.42–1.64)	0.86 (0.43–1.72)
No IUD	171 (29.0)	1108 (49.9)	1.00 (ref.)	1.00 (ref.)

* Adjusted for maternal age, BMI (with imputation), smoker (with imputation), induced abortion, fertility problems, and pre-existing diabetes.