Human Reproduction, Vol.26, No.8 pp. 2028–2035, 2011
Advanced Access publication on June 4, 2011 doi:10.1093/humrep/der156

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis

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Submitted on September 2, 2010; resubmitted on April 14, 2011; accepted on April 21, 2011

BACKGROUND: The relationship between the use of oral contraception (OC) and endometriosis remains controversial. We therefore compared various characteristics of OC use and the surgical diagnosis of endometriosis histologically graded as superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA) or deep infiltrating endometriosis (DIE).

METHODS: This cross-sectional study included 566 patients without visible endometriosis at surgery as controls, and 410 patients with histologically proven endometriosis, categorized by their worst lesions as SUP $n = 47$, OMA $n = 120$ and DIE $n = 243$. Personal data, including on OC use, were prospectively collected during standardized interviews. Statistical analysis was performed using unconditional logistic regression.

RESULTS: Past OC users had an increased incidence of endometriosis (adjusted odd ratios (OR) = 2.79, 95% confidence interval (CI) 1.74–5.12, $P = 0.002$) of any revised American Fertility Society stage. Women who had previously used OC for severe primary dysmenorrhea were even more frequently diagnosed with endometriosis (adjusted OR = 5.6, 95% CI 3.2–9.8), especially for DIE (adjusted OR = 16.2, 95% CI 7.8–35.3). Women who had previously used OC for other reasons also had an increased risk of endometriosis, but to a lesser extent (adjusted OR = 2.6, 95% CI 1.8–4.1). The age at which OC was initiated, duration of OC use and free interval from last OC use were not significantly different between control and endometriosis women, irrespective of histological grading. Current OC users did not show an increased prevalence of endometriosis (OR = 1.22, 95% CI 0.6–2.52).

CONCLUSIONS: Our data indicate that a history of OC use for severe primary dysmenorrhea is associated with surgical diagnosis of endometriosis, especially DIE, later in life. However, this does not necessarily mean that use of OC increases the risk of developing endometriosis. Past use of OC for primary dysmenorrhea may serve as a marker for women with endometriosis and DIE.

Key words: endometriosis / deep endometriosis / diagnosis / oral contraception / primary dysmenorrhea

Introduction

Endometriosis, histologically defined as functional endometrial glands and stroma developing outside of the uterine cavity (Sampson, 1927), is an enigmatic disease (Borghese *et al*., 2008; Bulun, 2009; Ngo *et al*., 2009) responsible for pelvic pain (Fauconnier and Chapron, 2005) and infertility (Matzuk and Lamb, 2008; de Ziegler *et al*., 2010). Public health wise, endometriosis is the source of an important economic burden (Gao *et al*., 2006). A common early clinical symptom of endometriosis is an enduring history of dysmenorrhea, which is often primary and severe (Momoeda *et al*., 2002).

Oral contraception (OC) is the treatment commonly offered to young women suffering from dysmenorrhea that is not adequately alleviated by non-steroidal anti-inflammatory drugs (NSAIDs) (Milsom *et al*., 1990; Harel, 2008). Suppressing ovarian function with OC improves the symptoms of dysmenorrhea (Group, 2005), but these classically recur upon stopping (Harada *et al*., 2008). Practically therefore, OC is often continued for several years (ACOG, 2005), as it has been shown to effectively prevent recurrence (Vercellini *et al*., 2008, 2010).

Not unexpectedly, the possibility of a link between OC use and endometriosis is a debated one (Hemmings *et al*., 2004; Missmer *et al*., 2004; Vercellini *et al*., 2011). In a case–control study, Parazzini *et al*., (1994) reported that using OC increases the risk of endometriosis. Conversely, other researchers observed, in a large cohort study, a lower risk of endometriosis amongst OC users (Vessey *et al*., 1993). Finally, still other studies failed to find any association between use of OC pills and endometriosis (Darrow *et al*., 1993; Heilier *et al*., 2007). We see two possible causes for these contradictory findings: (i) early reports (Darrow *et al*., 1993; Vessey *et al*., 1993; Calhaz-Jorge *et al*., 2004; Heilier *et al*., 2007) failed to mention for which indication OC was prescribed (Somigliana *et al*., 2011): treating severe primary dysmenorrhea, bleeding disorders, secondary dysmenorrhea and/or pelvic pain or simply for contraception; and (ii) in most prior studies, endometriosis was not histologically staged (Vessey *et al*., 1993; Parazzini *et al*., 1994; Hemmings *et al*., 2004).

Realizing that the link between endometriosis and OC use is still unclear, we undertook to reassess this issue while accounting for the two likely sources of confusion, the indication of OC and the histological staging of endometriosis. In the present study, we therefore determined whether OC has been used for treating severe primary dysmenorrhea or other reasons as well as other parameters pertinent to OC use. Moreover, endometriosis was histologically categorized as (i) superficial peritoneal endometriosis (SUP), (ii) ovarian endometrioma (OMA) or (iii) deep infiltrating endometriosis (DIE).

Materials and Methods

We conducted a cross-sectional study using data prospectively collected in all non-pregnant <42-year-old patients, who were surgically explored, by operative laparoscopy or laparotomy, for a benign gynecological indication at our institution between January 2004 and December 2008. Excluded from this population were women with cancer and/or who refused to consent to the study. Indications for surgery (possibly more than one per patient) included (i) pelvic pain defined as the presence, for at least 6 months, of dysmenorrhea and/or intermenstrual pelvic pain and/or dyspareunia of moderate to severe intensity (Fedele *et al*., 2005); (ii) infertility defined as at least 12 months of unprotected intercourse not resulting in pregnancy (Marcoux *et al*., 1997); (iii) pelvic mass (benign ovarian cysts, uterine myomas, etc.); and (iv) others: uterine bleeding, request for tubal ligation, infection, etc. Patients were considered as presenting endometriosis only when lesions were histologically proved. Patients visually diagnosed with endometriosis but without histological confirmation were excluded from the study (Chapron *et al*., 2010b).

Based on histological findings, endometriotic lesions were classified into three groups: SUP, OMA and DIE. DIE was histologically defined when the muscularis (bladder, intestine, ureter, etc.) was disturbed by endometriotic lesions (Chapron *et al*., 2010a). As these three types of endometriotic lesions are frequently associated (Somigliana *et al*., 2007), endometriotic patients were classified in the category of the worst finding. By definition, endometriotic lesions ranked from least to worst were SUP, OMA and DIE. For example, a patient presenting with SUP lesions associated with DIE nodules was classified as DIE (Chapron *et al*., 2010a). For the purpose of this study, patients were divided into two groups: Group A included patients without visual lesions of endometriosis, as checked during the operative procedure by a thorough examination of the abdominopelvic cavity (control group), and Group B included patients with histologically proven and graded endometriotic lesions (study group).

For each patient, data were collected in face-to-face interviews conducted by the surgeon during the month preceding surgery. For this, we used a structured previously published questionnaire (Chapron *et al*., 2010b). Briefly, for all patients we collected general information such as age, gravidity, parity, height, weight, body mass index (BMI), age of menarche, existence and duration of infertility, pelvic pain and lifestyle habits. Pelvic pain scores and associated symptoms (dysmenorrhea, deep dyspareunia, non-cyclic chronic pelvic pain, gastrointestinal symptoms and lower urinary tract symptoms) were assessed preoperatively using a visual analogue scale (Peveler *et al*., 1996). Gastrointestinal symptoms were defined as one or more of the following symptoms, either chronic or during menstruation: diarrhea, constipation, rectorrhagia, proctitis and colic rectal pain (Dousset *et al*., 2010). Similarly, lower urinary tract symptoms were defined as one or more of the following symptoms, either chronic or during menstruation: hematuria, recurrent urinary tract infections, pain on urinating, pollakiuria, non-microbial cystitis and dysuria (Fauconnier *et al*., 2002). For each patient, data regarding OC use were evaluated as follows: (i) never or ever OC use; (ii) characteristics of ever OC use: current or past use; (iii) indication for OC use: primary or secondary dysmenorrhea, menstrual disorders, contraception; (iv) age at onset of OC use; (v) duration of OC use; (vi) duration of free interval between OC use and diagnosis. Current OC use was defined as use of OC for at least 6 months before surgery, and past OC use was defined as no use of OC for at least 6 months before surgery (Narod *et al*., 2002; Modugno *et al*., 2004).

When present, the extent of endometriosis was staged according to the revised American Fertility Society (rAFS) classification (AFS, 1985). The mean rAFS scores (total, implants, adhesions) were assessed according to the same classification.

All statistical data were collected in a computerized database. Statistical analysis was performed using SPSS 13.0. The continuous data were presented as mean and mean standard deviation. Student's *t*-test was carried out when appropriate. The χ^2 or Fisher's exact tests were used for categorical data. Odd ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated for endometriosis and the types of endometriosis (SUP, OMA and DIE) compared with control group. We performed an unconditional logistic regression to control for potential confounding factors associated with OC prescription and endometriosis risk. We used a backward stepwise logistic regression analysis (Nick and Campbell, 2007) in which a *P* value of 0.5 was used as entry criteria; however, a *P* value of 0.2 was the threshold for the covariate staying in the model. A *P* value <0.05 was considered statistically significant.

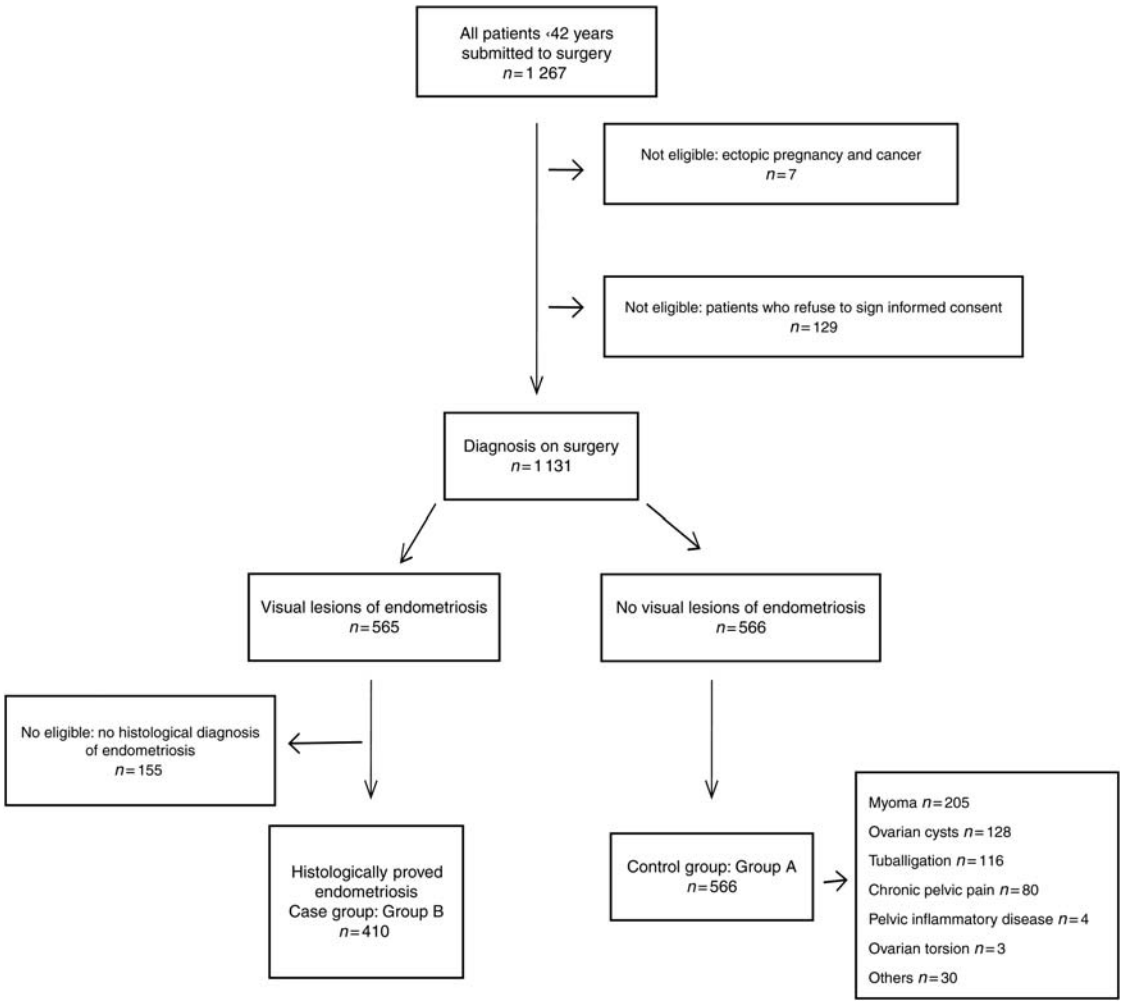

Figure 1 Flow chart showing longitudinal analysis of the study population.

The local ethics committee (CCPPRB: Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of our institution approved the study protocol and all the included patients signed an informed consent form.

Results

A diagram describing included patients is depicted in Fig. 1. Group A (control) included 566 patients without visual lesion of endometriosis at the time of the surgery. Group B (study) included 410 patients with histologically proven endometriosis at surgery. The patients' distribution according to their worst endometriotic lesion was as follows: SUP (47 patients, 11.4%), OMA (120 patients, 29.3%) and DIE (243 patients, 59.3%). Of 243 DIE patients, 87 (35.8%) presented associated OMAs (right 26, left 36 and bilateral 25). The total number of patients presenting with OMAs was 207 (50.5%). The extent of endometriosis according to rAFS stages was classified into the following groups: Stage I: 55 (13.4%) cases; Stage II: 85 (20.7%) cases; Stage III: 112 (27.3%) cases; and Stage IV: 158 (38.6%) cases. Mean rAFS scores were distributed as follows: total 37.1 ± 31.1, implants 15.7 ± 12.2 and adhesions 21.7 ± 24.7. Patient characteristics for cases and controls are presented in Table I. Differences were observed in gravidity, parity, weight, BMI, dysmenorrhea and preoperative pain scores. Conversely, age, height, age at menarche, infertility status and infertility duration were not significantly different between the two groups.

In the whole population, ever OC users had an increased prevalence of endometriosis as compared with women who never used OC (OR = 3.11, 95% CI 2.18–4.45, $P < 0.0001$). Both current and past OC users presented an increased risk of endometriosis when compared with never OC users (OR = 1.93, 95% CI 1.26–2.96, $P < 0.001$ and OR = 3.75, 95% CI 2.59–5.46, $P < 0.0001$, respectively). After running a multivariate analysis, we still found that ever and past OC users had an increased incidence of endometriosis compared with never users (adjusted OR = 2.17, 95% CI 1.19–3.95, $P = 0.012$ and adjusted OR = 2.79, 95% CI 1.74–5.12, $P = 0.002$, respectively). However, after logistic regression, current OC users did not show an increased prevalence of endometriosis when compared with never OC users (adjusted OR = 1.22, 95% CI 0.6–2.52, $P = 0.58$).

Table I Patients' characteristics between control and endometriosis groups.

Patients' characteristics	Group A ($n = 566$)	Group B ($n = 410$)	P
Age (years)[a]	32.18 ± 5.82	32.08 ± 5.46	0.78[d]
Gravidity (n, %)[a]	1. 01 ± 1.42	0.61 ± 1.08	<0.0001[d]
Parity (n, %)[a]	0.5 ± 0.99	0.3 ± 0.67	<0.0001[d]
Height (cm)[a]	167.9 ± 65.4	165.19 ± 7.07	0.39[d]
Weight (kg)[a]	63.8 ± 12.05	60.1 ± 10.46	<0.0001[d]
Body mass index (kg/m^2)[a]	23.33 ± 4.45	22.07 ± 3.92	<0.0001[d]
Age at menarche (years)[a]	12.92 ± 1.64	12.99 ± 1.61	0.5[d]
Infertility (n, %)	199 (35.2)	145 (35.4)	0.97[e]
Infertility duration (months)[a]	41.20 ± 29.16	43.23 ± 33.31	0.56[a]
Dysmenorrhea (n, %)			
No	222 (39.4)	38 (9.3)	
Primary	203 (36.1)	180 (44.2)	<0.0001[e]
Secondary	138 (24.5)	189 (46.4)	<0.0001[e]
Pain scores[a,b,c]			
Dysmenorrhea	3.92 ± 3.32	6.94 ± 2.72	<0.0001[d]
Deep dyspareunia	1.94 ± 3.55	4.46 ± 4.12	<0.0001[d]
Non-cyclic chronic pelvic pain	1.88 ± 2.91	3.2 ± 3.23	<0.0001[d]
Gastrointestinal symptoms	0.56 ± 1.71	3.81 ± 3.71	<0.0001[d]
Lower urinary tract symptoms	0.10 ± 0.8	1.11 ± 2.51	<0.0001[d]

[a]Data are presented as mean ± standard deviation.
[b]Sometimes more than one for the same patients.
[c]Visual analogue scale.
[d]Student t test.
[e]χ^2 test.

Results on OC uses according to the type of endometriotic lesions (SUP, OMA or DIE) are detailed in Table II. Compared with never users, ever and past OC users had, after adjustments, a significantly increased risk of SUP and DIE, whereas just a trend existed for OMAs. Conversely, the risk of endometriosis was not significantly increased for current OC users, for any type of endometriotic lesion. The age at which OC was initiated (19.4 ± 4.9 versus 18.4 ± 4.1 years; $P = 0.23$), duration of OC use (8.4 ± 5.5 versus 9.3 ± 5.3 years; $P = 0.12$) and free interval duration since OC use (5.6 ± 5.4 versus 5.1 ± 4.6 years; $p = 0.25$) were not significantly different between controls and cases. These results were also independent of the type of endometriotic lesion (SUP, OMA and DIE).

When considering OC use and endometriosis staged according to the rAFS classification, we observed that ever OC users and past users have an adjusted increased risk of endometriosis of all rAFS stages, compared with never users (Table III).

Results on OC use according to the indication for OC prescription and endometriosis are detailed in Table IV. Past OC use was associated with endometriosis whatever the indication for OC prescription. Past OC use prescribed because of the intensity of primary dysmenorrhea presented an increased risk of endometriosis (adjusted OR = 5.6, 95% CI 3.2–9.8). This result was observed for all rAFS stages: Stage I (adjusted OR = 8.4, 95% CI 2.7–32.2), Stage II (adjusted OR = 6.5, 95% CI 3.1–13.7), Stage III (adjusted OR = 4.9, 95% CI 2.2–11.1) and Stage IV (adjusted OR = 3.2, 95% CI 1.7–6.1) respectively. When previous OC use was indicated for another reason (secondary dysmenorrhea, menstrual disorders, contraception), the increased risk of endometriosis was still present although reduced (adjusted OR = 2.6, 95% CI 1.8–4.1). Previous OC use prescribed because of the intensity of primary dysmenorrhea presented an increased risk of DIE (adjusted OR = 16.2, 95% CI 7.8–35.3). When OC is prescribed for another reason, the risk of DIE is still present although greatly reduced (adjusted OR = 6.4, 95% CI 3.2–12.7).

Discussion

Banking on a large series of patients, our cross-sectional study revealed that past use of OC is associated with all rAFS stages of surgically confirmed endometriosis, but especially DIE. This association was the strongest if OC had been used in the past for treating severe primary dysmenorrhea. It remained nonetheless significant if OC had been used for another reason, as, for example, secondary dysmenorrhea, menstrual disorders or even contraception. Hence our results indicate that past OC exposure is associated with endometriosis. Conversely, we found no association between current OC use and endometriosis. These results are in agreement with the conclusions of Vercellini *et al.* whose meta-analysis claims that the incidence of endometriosis is decreased in current OC users but increased in past users (Vercellini *et al.*, 2011).

There are two primary strong points of our study: (i) All the patients (100%) were surgically explored and their lesions were analyzed histologically. In most series studying possible links between OC and endometriosis, diagnostic criteria for endometriosis were based on visualization at surgery (Vercellini *et al.*, 2011). Histological confirmation of endometriosis was obtained for all the patients in only two (Parazzini *et al.*, 1989; Westhoff *et al.*, 2000) of the 18 studies (11%) included in a recent review (Vercellini *et al.*, 2011). Together these two publications (Parazzini *et al.*, 1989; Westhoff *et al.*, 2000) merely represented only 8.5% of all endometriosis cases retained in the meta-analysis. (ii) Possible links between endometriosis and OC use were assessed according to the motives that led to using OC (primary or secondary dysmenorrhea, menstrual disorders, contraception), which were investigated prior to surgery (Table IV). Stratifying statistical analysis based on the initial indication for using OC rendered the interpretation more meaningful as well as better clinically rooted.

The other strong points of our study included the following. (i) The number of endometriosis cases included in our single series ($n = 410$) is important compared with the mean number of cases ($n = 279$) reported in the 18 series retained in the recent meta-analysis on OC and endometriosis (Vercellini *et al.*, 2011). (ii) After surgical removal of all endometriotic lesions, patients were classified according to the worst endometriotic lesion found. This methodological approach permitted us to analyze OC use according to the worst endometriotic lesion ranked from SUP, to OMA, to DIE, as confirmed

Table II Endometriosis risk according to OC use distribution and the most severe endometriotic lesion type.

	Group A control	Group B endometriosis type			Adjusted OR (95% CI)[a]		
	n = 566	SUP *n* = 47	OMA *n* = 120	DIE *n* = 243	Superficial	Endometrioma	Deep infiltrating
OC user							
Never user	160 (28.3)[b]	7 (14.9)	27 (22.5)	12 (4.9)			
Ever OC user	406 (71.7)	40 (85.1)	93 (77.5)	231 (95.1)	2.59 (1.11–6.03)	1.37 (0.84–2.23)	4.2 (1.54– 11.2)
Current user	142 (25.1)	13 (27.7)	25 (20.8)	41 (16.9)	2.7 (0.98–7.47)	0.95 (0.5–1.7)	1.98 (0.65–6.07)
Past user	264 (46.6)	27 (57.4)	68 (56.7)	190 (78.2)	2.56 (1.07–6.09)	1.65 (0.99–2.75)	5.7 (2.1–15.7)

OC, oral contraception; SUP, superficial endometriosis; OMA, ovarian endometrioma; DIE, deeply infiltrating endometriosis.
[a]OC use was adjusted for age, gravidity, infertility, dysmenorrhea and OC use for primary dysmenorrhea.
[b]Reference category for odds ratio adjusted on logistic regression.

Table III Endometriosis risk according to OC use and rAFS stages.

	Group A control	Group B rAFS stage				Adjusted OR (95% CI)[a]			
		I	II	III	IV	I	II	III	IV
(*n*, %)	*n* = 566	*n* = 55	*n* = 85	*n* = 112	*n* = 158				
Never OC user	160 (28.3)[b]	4 (7.3)	5 (5.9)	14 (12.5)	23 (14.6)				
Ever OC user	406 (71.7)	51 (92.7)	80 (94.1)	98 (87.5)	135 (85.4)	4.9 (1.75–13.86)	7.8 (2.84–21.87)	2.73 (1.5–4.9)	2.29 (1.4–3.7)
Current user[a]	142 (25.1)	17 (30.9)	23 (27.1)	24 (21.4)	16 (9.6)	4.8 (1.6–14.6)	6.5 (2.2–19.2)	1.8 (0.9–3.7)	0.7 (0.4–1.5)
Past user[a]	264 (46.6)	34 (61.8)	57 (67.0)	74 (66.1)	119 (75.8)	5.0 (1.7–14.4)	8.6 (3.07–24.2)	3.2 (1.7–5.9)	3.1 (1.9–5.1)

OC: oral contraception.
[a]OC use adjusted for age, gravidity, infertility and OC use for primary dysmenorrhea.
[b]Reference category for odds ratio adjusted on logistic regression.

Table IV Endometriosis risk according to the indication for oral contraceptive use prescription.

(A)	Control *N* = 566	Endometriosis, *N* = 410	OR adjusted[a]
No previous OC use	160 (28.3)[b]	46 (11.2)	
Previous OC use to treat severe primary DM	37 (6.5)	78 (19)	5.6 (3.2–9.8)
Previous OC use indicated for other indications	369 (65.2)	286 (69.8)	2.6 (1.8–4.1)

(B)	Control *N* = 566	Endometriosis			OR adjusted[a]		
		SUP *N* = 47	OMA *N* = 120	DIE *N* = 243	SUP	OMA	DIE
No previous OC use	160 (28.3)[b]	7 (14.9)	27 (22.5)	12 (4.9)			
Previous OC use to treat severe primary DM	37 (6.5)	6 (12.8)	15 (12.5)	57 (23.5)	3.5 (0.9–13.5)	1.9 (0.8–4.3)	16.2 (7.8–35.3)
Previous OC use indicated for other indications	369 (65.2)	34 (72.3)	78 (65)	174 (71.6)	2.8 (1.1–7.1)	1.3 (0.8–2.1)	6.4 (3.2–12.7)

OC: oral contraception; DM: dysmenorrhea.
[a]Variables evaluated on regression: age, gravidity, infertility.
[b]Reference category for adjusted odds ratio on logistic regression.

histologically. (iii) Control and study groups underwent similar questioning during the month preceding surgery. Furthermore, they were explored surgically by the same team of surgeons experienced in treating endometriosis. (iv) This study divided ever OC users into two separated groups of 'past' and 'current' users. This methodological point is essential, because if these two groups had not been individualized a primary element of the links existing between OC use and endometriosis would have been missed. (v) Our data shed light on numerous parameters pertaining to OC use in its relationship with endometriosis: age at onset, duration of use, free interval from OC use and reason (medical indication) for OC use. Finally, our methodological approach for identifying a control population is of crucial importance as this too may affect findings (Treloar *et al*., 2010), and constitutes a common cause of biases in epidemiological studies on endometriosis (Holt and Weiss, 2000; Zondervan *et al*., 2002; Buck Louis *et al*., 2007).

In spite of all the precautions taken, our study may be still subject to certain shortcomings and/or biases. (i) Selection biases may have occurred because OC is frequently prescribed as first-line treatment for dysmenorrhea, a symptom strongly associated with endometriosis. Therefore we may have recruited an excess of patients who failed medical treatment and need surgery. Unfortunately, these possible selection biases cannot be adjusted by any multivariate analysis. This important problem is however not unique but rather common to all cross-sectional studies on the relationship between OC use and risk of endometriosis. (ii) Recall biases may have been involved. Even though data were collected prospectively (before knowing the histological outcome), epidemiological information, notably concerning OC use, was retrospective in nature, being recounted long after the facts. Endometriosis patients and surgeons alike are most often suspicious of the diagnosis preoperatively. This could theoretically lead to biases in how cases and controls were questioned. Hence, the risks of reporting errors must be acknowledged (Treloar *et al*., 2010). (iii) Reverse causality bias may be introduced in cross-sectional studies because exposure is ascertained at the same point in time as the outcome. Consequently, because the true time sequence of events is unknown, we cannot ascertain that exposure preceded outcome. (iv) However structured (Chapron *et al*., 2010b), our questionnaire provided no information on the type of OC administration (cyclical or continuous) used. (v) Infertility, typically associated with endometriosis, could constitute a bias for lesser OC use in this group. Fortunately however, the incidence and duration of infertility did not differ between the study group and controls (Table I).

Our finding of an association between OC use and endometriosis calls for the following two comments: (i) Our findings do not necessarily mean that OC use actually led to the development of endometriosis. An association does not constitute a proof of cause. The possibility that the observed link is not a causal one is stressed by the two following observations: firstly, hormonal therapies are truly indicated in endometriosis and effective on symptoms (Vercellini *et al*., 2003; Sesti *et al*., 2007; Harada *et al*., 2008; Seracchioli *et al*., 2009, 2010), and secondly dysmenorrhea as a reason to initiate OC use was more frequent among endometriotic patients (Somigliana *et al*., 2011). Hence, the association would not constitute a proof of cause and effect. It may only point to the fact that women who receive OC for dysmenorrhea may already have developed endometriosis, but it is still undiagnosed (Somigliana *et al*., 2011). (ii) The observation in a patient that primary dysmenorrhea does not subside with either NSAIDs or OC may help to single out people who are prone to developing endometriosis and especially DIE (Chapron *et al*., 2011). Our results stress therefore the need to question about past OC use, especially for severe primary dysmenorrhea, each time endometriosis is suspected.

In conclusion, our cross-sectional study banking on prospectively obtained data in 976 surgically explored women identified that past, but not current, OC use is associated with endometriosis, and especially with DIE. This association exists irrespective of the reason for OC use but is the strongest, especially in the case of DIE, if OC was used for treating severe primary dysmenorrhea. This observed association does not mean however that OC use increases the risk of endometriosis. Possible confounding factors must be taken into account when interpreting data. Future prospective studies should determine whether OC use is merely a marker for people at risk of developing endometriosis, and especially DIE, or actually instrumental in the development of endometriosis.

Authors' roles

C.C. and D.d.Z. conceived and designed the study. C.S., C.C., D.d.Z. and M.-C.L.-P. analyzed and interpreted the data. F.G. supervised and reviewed all the statistical analysis. C.C., C.S., B.B., M.-C.L.-P. and P.S. contributed to data collection and performed surgical procedures. All the authors contributed to writing the manuscript. All the authors approved the final version of the manuscript.

Acknowledgements

The authors warmly thank surgeons from our department for their expert assistance with data collection. The authors also thank Nathalie Girma for unabatedly managing the patient database.

Conflict of interest

D.d.Z. owns equity in Ultrast LLC, and has served on advisory boards for IBSA and IPSEN Pharmaceuticals.

References

ACOG. ACOG Committee Opinion. Number 310, April 2005. Endometriosis in adolescents. *Obstet Gynecol* 2005;**105**:921–927.

AFS. Revised American Fertility Society classification of endometriosis: 1985. *Fertil Steril* 1985;**43**:351–352.

Borghese B, Mondon F, Noel JC, Fayt I, Mignot TM, Vaiman D, Chapron C. Gene expression profile for ectopic versus eutopic endometrium provides new insights into endometriosis oncogenic potential. *Mol Endocrinol* 2008;**22**:2557–2562.

Buck Louis GM, Hediger ML, Pena JB. Intrauterine exposures and risk of endometriosis. *Hum Reprod* 2007;**22**:3232–3236.

Bulun SE. Endometriosis. *N Engl J Med* 2009;**360**:268–279.

Calhaz-Jorge C, Mol BW, Nunes J, Costa AP. Clinical predictive factors for endometriosis in a Portuguese infertile population. *Hum Reprod* 2004; **19**:2126–2131.

Chapron C, Bourret A, Chopin N, Dousset B, Leconte M, Amsellem-Ouazana D, de Ziegler D, Borghese B. Surgery for bladder endometriosis: long-term results and concomitant management of associated posterior deep lesions. *Hum Reprod* 2010a;**25**:884–889.

Chapron C, Souza C, de Ziegler D, Lafay-Pillet MC, Ngo C, Bijaoui G, Goffinet F, Borghese B. Smoking habits of 411 women with histologically proven endometriosis and 567 unaffected women. *Fertil Steril* 2010b;**94**:2353–2355.

Chapron C, Lafay-Pillet MC, Monceau E, Borghese B, Ngo C, Souza C, de Ziegler D. Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis. *Fertil Steril* 2011;**95**:877–881.

Darrow SL, Vena JE, Batt RE, Zielezny MA, Michalek AM, Selman S. Menstrual cycle characteristics and the risk of endometriosis. *Epidemiology* 1993;**4**:135–142.

de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet* 2010;**376**:730–738.

Dousset B, Leconte M, Borghese B, Millischer AE, Roseau G, Arkwright S, Chapron C. Complete surgery for low rectal endometriosis: long-term results of a 100-case prospective study. *Ann Surg* 2010; **251**:887–895.

Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. *Hum Reprod Update* 2005; **11**:595–606.

Fauconnier A, Chapron C, Dubuisson JB, Vieira M, Dousset B, Breart G. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. *Fertil Steril* 2002;**78**:719–726.

Fedele L, Bianchi S, Zanconato G, Bergamini V, Berlanda N, Carmignani L. Long-term follow-up after conservative surgery for bladder endometriosis. *Fertil Steril* 2005;**83**:1729–1733.

Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril* 2006;**86**:1561–1572.

Group TECW. Noncontraceptive health benefits of combined oral contraception. *Hum Reprod Update* 2005;**11**:513–525.

Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. *Fertil Steril* 2008;**90**:1583–1588.

Harel Z. Dysmenorrhea in adolescents and young adults: from pathophysiology to pharmacological treatments and management strategies. *Expert Opin Pharmacother* 2008;**9**:2661–2672.

Heilier JF, Donnez J, Nackers F, Rousseau R, Verougstraete V, Rosenkranz K, Donnez O, Grandjean F, Lison D, Tonglet R. Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study. *Environ Res* 2007;**103**:121–129.

Hemmings R, Rivard M, Olive DL, Poliquin-Fleury J, Gagne D, Hugo P, Gosselin D. Evaluation of risk factors associated with endometriosis. *Fertil Steril* 2004;**81**:1513–1521.

Holt VL, Weiss NS. Recommendations for the design of epidemiologic studies of endometriosis. *Epidemiology* 2000;**11**:654–659.

Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. *N Engl J Med* 1997;**337**:217–222.

Matzuk MM, Lamb DJ. The biology of infertility: research advances and clinical challenges. *Nat Med* 2008;**14**:1197–1213.

Milsom I, Sundell G, Andersch B. The influence of different combined oral contraceptives on the prevalence and severity of dysmenorrhea. *Contraception* 1990;**42**:497–506.

Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, Hunter DJ. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 2004;**104**:965–974.

Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004;**191**:733–740.

Momoeda M, Taketani Y, Terakawa N, Hoshiai H, Tanaka K, Tsutsumi O, Osuga Y, Maruyama M, Harada T, Obata K *et al.*. Is endometriosis really associated with pain? *Gynecol Obstet Invest* 2002;**54**(Suppl 1):18–21; discussion 21–13.

Narod SA, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Robson M *et al.* Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2002;**94**:1773–1779.

Ngo C, Chereau C, Nicco C, Weill B, Chapron C, Batteux F. Reactive oxygen species controls endometriosis progression. *Am J Pathol* 2009; **175**:225–234.

Nick TG, Campbell KM. Logistic regression. *Methods Mol Biol* 2007; **404**:273–301.

Parazzini F, La Vecchia C, Franceschi S, Negri E, Cecchetti G. Risk factors for endometrioid, mucinous and serous benign ovarian cysts. *Int J Epidemiol* 1989;**18**:108–112.

Parazzini F, Ferraroni M, Bocciolone L, Tozzi L, Rubessa S, La Vecchia C. Contraceptive methods and risk of pelvic endometriosis. *Contraception* 1994;**49**:47–55.

Peveler R, Edwards J, Daddow J, Thomas E. Psychosocial factors and chronic pelvic pain: a comparison of women with endometriosis and with unexplained pain. *J Psychosom Res* 1996;**40**:305–315.

Sampson JA. Peritoneal endometriosis due to premenstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927;**14**:46.

Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frasca C, Elmakky A, Venturoli S. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. *Hum Reprod* 2009;**24**:2729–2735.

Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. *Fertil Steril* 2010;**94**:464–471.

Sesti F, Pietropolli A, Capozzolo T, Broccoli P, Pierangeli S, Bollea MR, Piccione E. Hormonal suppression treatment or dietary therapy versus placebo in the control of painful symptoms after conservative surgery for endometriosis stage III–IV. A randomized comparative trial. *Fertil Steril* 2007;**88**:1541–1547.

Somigliana E, Vercellini P, Gattei U, Chopin N, Chiodo I, Chapron C. Bladder endometriosis: getting closer and closer to the unifying metastatic hypothesis. *Fertil Steril* 2007;**87**:1287–1290.

Somigliana E, Vercellini P, Vigano P, Abbiati A, Benaglia L, Fedele L. Endometriosis and estroprogestins: the chicken or the egg causality dilemma. *Fertil Steril* 2011;**95**:431–433.

Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. *Am J Obstet Gynecol* 2010;**202**:534 e531–534 e536.

Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril* 2003;**80**:560–563.

Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. *Am J Obstet Gynecol* 2008;**198**:504 e501–505.

Vercellini P, Somigliana E, Vigano P, De Matteis S, Barbara G, Fedele L. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. *Reprod Biomed Online* 2010;**21**:259–265.

Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A, Fedele L. Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. *Hum Reprod Update* 2011;**17**:159–170.

Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. *BMJ* 1993; **306**:182–184.

Westhoff C, Britton JA, Gammon MD, Wright T, Kelsey JL. Oral contraceptive and benign ovarian tumors. *Am J Epidemiol* 2000; **152**:242–246.

Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. *Hum Reprod* 2002;**17**:1415–1423.