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Deep infiltrating endometriosis is associated with markedly lower body mass index: a 476 case–control study

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BACKGROUND: An inverse association between BMI and endometriosis has been reported but remains controversial. We decided to evaluate the association between BMI and the different types of endometriosis, classified as superficial endometriosis (SUP), deep infiltrating endometriosis (DIE) and ovarian endometrioma (OMA).

METHODS: From a prospective database of patients who underwent gynecological surgery between February 2005 and October 2008, we compared 238 patients with a histological diagnosis of endometriosis to 238 age- and smoking-status-matched controls using a prospective preoperative questionnaire and surgical data. Numerical variables means were compared for matched pairs, and non-parametric variables using Wilcoxon test. The Odds ratios for all types of endometriosis adjusted for confounding variables were computed according to predefined BMI groups [1($<$18.5), 2 ($\geq$18.5 and $<$22), 3($\geq$22 and $<$25), 4($\geq$25)], taking Group 3 as the reference population.

RESULTS: BMI was significantly lower for all 238 patients (21.70 $\pm$ 3.7 versus 23.29 $\pm$ 4.1, $P < 0.001$), for 101 OMA patients (21.88 $\pm$ 3.8 versus 22.99 $\pm$ 4, $P < 0.038$), and for 97 DIE patients (21.35 $\pm$ 3.4 versus 23.35 $\pm$ 3.8, $P < 0.001$) compared with their own controls, but not for the 40 SUP patients. Patients in Group 1 had adjusted odds ratios as high as 3.3 [95% confidence interval (CI): 1.6–6.8] for DIE and 2.7 (95% CI: 1.1–6.8) for OMA; in Group 2, the adjusted oddd ratios were 2.6 (95% CI: 1.3–5.5) for DIE and 2.9 (95% CI: 1.5–5.4) for OMA.

CONCLUSIONS: Endometriotic patients have lower BMI than age- and smoking-status-matched controls, independent of confounding variables. Patients with the lowest BMI ($<$18.5) are at a high risk of DIE.

Key words: endometriosis / body mass / deep infiltrating endometriosis / logistic regression analysis

Introduction

Endometriosis, defined as the presence of endometrial tissue (gland and stroma) outside of the uterus (Sampson, 1927), mainly causes pain (Chapron *et al.*, 2003; Fauconnier and Chapron, 2005) and infertility (de Ziegler Lancet *et al.*, 2010). Irrespective of the type of economic healthcare system, the disease is characterized by a long delay in being diagnosed (Greene *et al.*, 2009) particularly, in case of deep infiltrating endometriosis (DIE) (Matsuzaki *et al.*, 2006). It is however reasonable to think that if endometriosis could be diagnosed earlier, its surgical management would be less extensive and potentially less damaging and less risky.

Clinical questioning is the first step of the diagnosis-making process. It normally precedes the physical examination and the deployment of diagnostic aides such as imaging procedures and blood measurements. Clinical questioning is essential for two main reasons. First, questioning is simple, cost-effective and a helpful step in the diagnosis process of endometriosis. Questioning normally searches for: (i) sets of sociodemographic data, lifestyle characteristics and medical and reproductive history that are associated with endometriosis (Cramer and Missmer, 2002; Giudice and Kao, 2004; Sinaii *et al.*, 2008); (ii) painful symptoms that are correlated to the anatomic locations of DIE nodules (Fauconnier *et al.*, 2002) and contribute to diagnosing endometriosis of the bladder detrusor (Fedele *et al.*, 2007) or

posterior DIE (Chapron et al., 2005); and (iii) the patients' history of events occurring at adolescence that may be associated with DIE (Chapron et al., 2011a,b). Second, epidemiological data are crucial for better understanding the pathogenesis of endometriosis (Vigano et al., 2004).

BMI is a parameter easily obtained at the time of clinical questioning. The possibility of relationships between endometriosis and BMI is controversial however. Some authors (Cramer et al., 1986; Darrow et al., 1993; Sangi-Haghpeykar and Poindexter, 1995; Moën and Schei, 1997; Signorello et al., 1997; Hemmings et al., 2004) found either no association or barely a trend between low BMI and endometriosis at the time of diagnosis. Others however demonstrated a significant correlation between low BMI and endometriosis (McCann et al., 1993; Berube et al., 1998; Missmer et al., 2004; Ferrero et al., 2005; Hediger et al., 2005; Matalliotakis et al., 2008; Parazzini et al., 2008). We believe that these seemingly contradictory results are mainly due to two reasons: (i) in many past epidemiological studies on endometriosis, the disease was not histologically diagnosed and/or staged (Darrow et al., 1993; Sangi-Haghpeykar and Poindexter, 1995; Hemmings et al., 2004); and (ii) endometriosis is an heterogeneous disease and three types of disease must be considered (Nisolle and Donnez, 1997): superficial endometriosis (SUP), ovarian endometrioma (OMA) and DIE.

In order to elucidate this point, we evaluated a large series of endometriosis cases for links existing between BMI and endometriosis histologically diagnosed and staged as SUP, OMA or DIE.

Materials and Methods

Between January 2005 and October 2008, we conducted a case–control study using a database of prospectively acquired characteristics. It included all women aged younger than 42 years who are undergoing surgery (by laparoscopy or laparotomy) at our institution for gynecological pathologies, excluding only: (i) patients with previous history of surgery for endometriosis; (ii) patients operated for cancer and (iii) pregnant patients (i.e. ectopic pregnancies). We also excluded from study participation patients who refused to sign the consent form and those whose surgical excision was considered as incomplete by the surgeon. Indications for surgery, sometimes more than one for one patient, were the following: (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., 2007); (ii) infertility defined as at least 12 months of unprotected intercourse not resulting in pregnancy (Marcoux et al., 1997); (iii) pelvic mass (benign ovarian mass, uterine myoma, etc.); (iv) others: uterine bleeding, request for tubal ligation, adnexal torsion, infection, etc.

For the purpose of this study, patients retained for analysis were divided into two groups: Group A (study group) included patients with histologically proved endometriotic lesions, and Group B (control group) included patients without any visual lesions of endometriosis as checked during the surgical procedure. Patients visually diagnosed with endometriosis but without histological confirmation were considered to be ineligible for the study (Chapron et al., 2010). Histologically proved endometriotic lesions were classified into three groups: SUP, OMA and deeply infiltrating endometriosis (DIE) (Chapron et al., 2010). DIE was histologically defined as endometriotic lesions that infiltrate the muscularis propria (bladder, intestine, uretere) (Chapron et al., 2010). DIE lesions were classified according to five locations: bladder, uterosacral ligament(s), vagina, intestine and uretere (Chapron et al., 2006). Because the three types of endometriotic lesions (SUP, OMA and DIE) were frequently associated (Somigliana et al., 2007), endometriotic patients were arbitrarily classified from least to worst as follows: SUP, OMA and DIE (Chapron et al., 2010). During the surgery, stages and mean scores (total, implants, adhesions) were assessed according to the revised American Fertility Society (rAFS) (1985).

For each patient, data were recorded during face-to-face interviews using a structured, previously published questionnaire (Chapron et al., 2010). Interviews were conducted by the surgeon during the month preceding the surgery. The following data were collected: age, parity, gravidity, height, weight, infertility (primary or secondary), gynecologic pelvic pain symptoms (dysmenorrhea, deep dyspareunia, non-cyclic chronic pelvic pain), gastro-intestinal symptoms (Dousset et al., 2010), lower urinary tract symptoms (Fauconnier et al., 2002), oral contraceptive (OC) use (Vercellini et al., 2011) and smoking habits (Signorello et al., 1997). For each painful symptom, intensity was assessed using a 10-cm visual analogue scale (VAS) (Peveler et al., 1996). Patients were arbitrarily divided into two groups depending on pre-operative pain symptoms intensity: moderate < 7 and severe ≥ 7 (Anaf et al., 2006). Data regarding OC use were evaluated as follows: (i) never or ever OC use and (ii) characteristics of ever OC use: current or past users (Chapron et al., 2011b). The smoking habits were recorded in three categories (never, current or past smokers) in accordance with the previous studies (Chapron et al., 2010). Age was divided into four intervals: <25, 25–29, 30–34 and ≥ 35 (Vercellini et al., 2007).

BMI was calculated as weight (kg) divided by the square of height (m^2). According to WHO's expert committee (1995), the weight status is classified into five groups: underweight ($BMI < 18.5$), normal weight ($18.5 \leq BMI \leq 24.9$), overweight ($25 \leq BMI \leq 29.9$), obesity ($30 \leq BMI < 40$) and morbid obesity ($BMI \geq 40$). We divided the normal weight group into two intervals around the limit of 22 (Jacobson et al., 2006) to evaluate the influence of BMI variations on the risk of endometriosis in the normal range of the general population. We put together in the same group overweight and obese patients (Seidell and Flegal, 1997; Chen et al., 2010). So for this study, women were categorized according to BMI as follows: Group 1: $BMI < 18.5$; Group 2: $18.5 \leq BMI \leq 21.9$; Group 3: $22 \leq BMI \leq 24.9$; Group 4: $BMI \geq 25$.

Statistical analysis

Cases with endometriosis were matched to the next disease-free chronologically occurring patient who belonged to the same age interval and smoking habits group.

Means of BMI were compared for matched pairs of cases and their controls. All subgroups of endometriosis based on anatomic classification (Chapron et al., 2006) (SUP, OMA and DIE) and disease severity (rAFS classification, 1985) were compared with their own controls. The difference between non-parametric variables was assessed by Wilcoxon test. Women were categorized according to BMI into four groups and we computed, in these groups, the crude and multivariate adjusted odds ratio (ORa) and the corresponding 95% confidence interval (CI) for the risk of endometriosis, DIE and OMA compared with the reference group: for these analyses, women with $22 \leq BMI \leq 24.9$ (Group 3) served as the reference population. Potentially confounding variables [(gastro-intestinal pains (VAS ≥ 7), chronic pelvic pain (VAS ≥ 7), parity (nulliparity or ≥ 1 pregnancy), OC use (never or ever) and infertility at the time of surgery (yes or no))] were introduced in the model (Greenland, 1989). Infertility and chronic pelvic pain did not significantly affect the results and were not retained in the final model. As patients were matched for age and smoking habits, age and cigarette smoking history were introduced in the model as forced variables (Holford, 1978). We used age, smoking and multivariate-adjusted logistic regression with maximum likehood fitting for obtaining ORa and the 95% CI for the risk of endometriosis, OMA and DIE (Bland and Altman, 1994; Nick and Campbell, 2007) when compared with the reference group. We conducted all analyses

using Statistical Package for the Social Sciences for Windows version 14.0 (SPSS Inc., Chicago, IL, USA). A *P*-value of <0.05 was considered as statistically significant. The local Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biologique) at our institution approved the study protocol and each patient included signed an informed consent form.

Results

During the study period, 290 patients had a first-time intervention for histologically proved endometriosis. Of these, 20 patients (6.9%) were excluded because surgical treatment was considered as incomplete, as were 32 others (11.0%) who did not sign an informed consent. Finally, 238 endometriotic patients (Group A) were included for statistical analysis after having been matched to controls (Group B) as defined already. Indications for surgery in the control group, sometimes more than one for the same patient, were the following: benign ovarian cysts (60 cases; 25.2%), myomas (83 cases; 34.9%), pelvic pain (34 cases; 14.3%), tubal infertility (50 cases; 21.0%) and others (17 cases; 7.1%). For patients with histologically proved endometriosis, classifications and mean scores according to rAFS Classifications (1985) are detailed in Table I. The distribution of endometriotic patients according to the worst endometriotic lesion was as follows: SUP (40 patients; 16.8%), OMA (101 patients; 42.4%) and DIE (97 patients; 40.8%). The distribution of endometriotic lesions is detailed in Table I. Patients' epidemiological characteristics in study and control groups are detailed in Table II.

Taken together, all endometriotic patients had a lower mean BMI than controls (21.7 ± 3.7 versus 23.3 ± 4.11, $P < 0.0001$) (Fig. 1). For DIE and OMA patients, the mean BMI was significantly lower than that of their matched controls, at 21.3 ± 3.4 versus 23.3 ± 3.8 ($P < 0.001$) and 21.9 ± 3.84 versus 23.0 ± 4.07 ($P < 0.038$), respectively. For SUP patients, the difference with controls did not reach the level of significance (22.1 ± 4.0 versus 23.9 ± 5.0, $P < 0.098$).

The distribution of patients in the four predefined BMI groups (Fig. 2) shows that the majority of DIE and OMA patients belong to the lowest BMI groups. For DIE patients, 15.5% of DIE were in Group 1 (BMI $<$ 18.5) when compared with 7.6% for their matched controls ($P < 0.0001$). Moreover, 53.6% of DIE were in Group 2, when compared with 35.4% for controls ($P < 0.0001$). For the population of patients with OMA, there were respectively 11.9 and 53% of patients in Group 1 and 2 compared with 6.9 and 42.6% for their matched controls, respectively ($P < 0.04$). There was no significant difference in distribution amongst the four groups of BMI between SUP patients and their controls.

The crude OR and the OR adjusted for confounding variables (gastrointestinal and chronic pelvic pain, parity and oral contraception use) for having endometriosis, DIE or OMA compared with the reference group ($22 \leq$ BMI ≤ 24.5) are summarized in Table III. For the lowest BMI values (Group 1: BMI $<$ 18.5), the ORa of having DIE was 3.3 (95% CI: 1.6–6.8), while for OMA, the ORa was 2.7 (95% CI: 1.1–6.1). The ORa of DIE according to the BMI groups are successively 3.3 (95% CI: 1.3–8.8) for Group 1, 2.6 (95% CI: 1.3–5.5) for Group 2 and 0.8 (95% CI: 0.3–2.1) for Group 4 (Fig. 3). As For the lowest BMI values (Group 1: BMI $<$ 18.5) the adjusted OR to have a DIE compared with the reference group ($18.5 \leq$ BMI ≤ 21.9) was 3.3 (95% CI: 1.6–6.8).

For the BMI values in the normal range of the general population (Groups 2 and 3), patients in Group 2 ($18.5 \leq$ BMI ≤ 21.9) were at higher risk of DIE [ORa: 2.6 (95% CI: 1.3–5.5)] and of OMA [ORa: 2.9 (95% CI: 1.5–5.4)], when compared with patients in Group 3.

For the lowest BMI ($<$18.5), if we consider the severity of endometriosis evaluated by the rAFS score, the ORa of having stage I–II endometriosis was 3.3 (95% CI: 1.25–9.43) and the adjusted OR of having stage III–IV disease was 4.0 (95% CI: 1.6–10.3).

Table I Characteristics of the population with endometriosis.

Patients' characteristics	*N*	Data
rAFS classification (*n*,%)		
I	43	18%
II	46	19%
III	92	39%
IV	57	24%
rAFS scores[a]		
Adhesions		13.20 ± 18.6
Implant		15.45 ± 11.6
Total		28.39 ± 25.1
Distribution according to the worst endometriotic lesion[b]		
DIE (*n*, %)	97	40.80%
OMA (*n*, %)		
Total	130	
Right	46	
Left	53	
Bilateral	31	
With no DIE	101	42.4%
Right	37	
Left	40	
Bilateral	24	
With DIE	29	
SUP (*n*, %)		
Total	61	
No DIE and No OME	40	16.8%
Distribution according to the main DIE lesions (*n*, %)[c]		
Utero-sacral ligaments	29	12%
Vagina	15	6%
Bladder	11	5%
Intestine	34	14%
Ureter	8	3%

SUP, superficial peritoneal endometriosis; OMA, ovarianendometrioma; DIE, Deep infiltrating endometriosis.
[a]According to the rAFS classification (1985).
[b]According to a previously published classification of endometriotic lesions (Chapron *et al.*, 2010).
[c]According to a previously published surgical classification for deep endometriosis (Chapron *et al.*, 2003).

Discussion

We observed after adjustment for pain scores, parity and OC use that women with surgically confirmed and histologically staged endometriosis had lower BMI than controls matched for age and smoking

Table II Patients' characteristics in control and endometriosis groups matched on age and smoking habits.

	Endometriosis (*N* = 238)	Controls (*N* = 238)	*T* or Wilcoxon test
Age (years)[a]	31.5 ± 5.3	31.4 ± 5.2	NS
Age intervals (*n*, %)			
<25	18 (7.6)	18 (7.6)	Matched variable
25–29	74 (31.1)	74 (31.1)	
30–34	75 (31.5)	75 (31.5)	
≥35	71 (29.8)	71 (29.8)	
Smoking status (*n*, %)			
Never	130 (54.6)	130 (54.6)	Matched variable
Former	35 (14.7)	35 (14.7)	
Current	73 (30.7)	73 (30.7)	
Weight (kg)[a]	59.1 ± 9.8	63.6 ± 11.3	0.001
Height (cm)[a]	165.2 ± 6.3	165.43 ± 6.2	NS
BMI (kg/m^2)[a]	21.7 ± 3.7	23.3 ± 4.1	0.001
Parity	0.2 ± 0.6	0.5 ± 1.0	0.001
Gestity	0.5 ± 0.9	1 ± 1.4	0.001
Preoperative painful symptoms scores[a,b]			
VAS DM	6.2 ± 2.5	3.8 ± 3.4	0.001
VAS DP	3.6 ± 3.4	1.7 ± 2.7	0.001
VAS CPP	2.5 ± 3	1.8 ± 2.9	0.019
VAS GI	2.7 ± 3.5	0.7 ± 1.8	0.001
VAS LUT	1 ± 2.5	0.1 ± 0.8	0.001
OC use (*n*, %)			
Never	33 (13.9)	65 (27.4)	0.001
Former	150 (63.0)	108 (45.6)	
Current	55 (23.1)	64 (27.0)	
Infertility (*n*, %)			
No	163 (68.5)	160 (67.2)	0.001
Primary	57 (23.9)	34 (14.3)	
Secondary	18 (7.6)	44 (18.5)	

VAS, Visual analogue scale; OC, oral contraceptive; DM, dysmenorrhea; DP, deep dyspareunia; CPP, chronic pelvic pain; GI, gastrointestinal symptoms; LUT, lower urinary tract symptoms.
[a]Data are presented as mean ± standard deviation.
[b]Sometimes more than one for the same patient.

habits. Looking at different subgroups of endometriosis, we found that the ORa for DIE was increased in lower BMI ranges, a difference not reaching the level of significance for SUP. An inverse association was found between DIE and BMI, even within the normal BMI range, with the lowest BMI values being associated with a high risk of endometriosis.

These results are in agreement with other studies in which the case population was similarly selected, based on surgical diagnosis and with a high prevalence of severe forms of endometriosis. Ferrero *et al.* (2005) found a significant difference between the BMI of endometriotic patients and controls in their population of histologically diagnosed endometriosis, which, like ours, showed a high prevalence of severe endometriosis. Likewise, Hediger *et al.* (2005) found that endometriosis

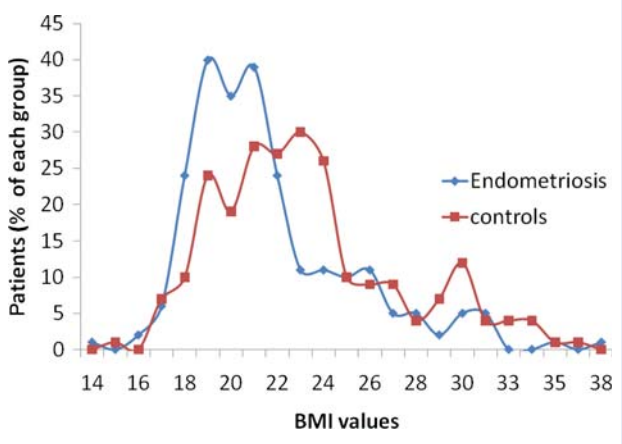

Figure 1 Repartition of BMI values for endometriosis patients and controls matched on age and smoking habits.

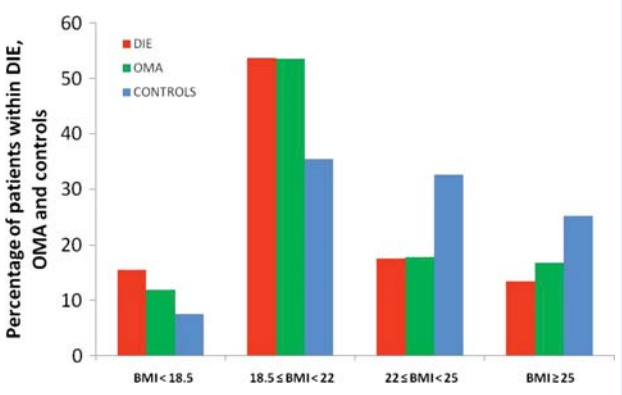

Figure 2 Distribution of women with endometriosis and controls according to BMI categories.

was associated with low BMI, and also observed, when stratifying cases by severity of disease, that patients with advanced disease have even lower BMI values. Taken together, these results underpin an inverse correlation between BMI and endometriosis.

Conversely, authors who did not find that the BMI was significantly lower in endometriosis most often studied populations in whom no histological diagnosis was performed, had low incidences of severe forms and/or made comparisons to control populations in whom endometriosis was not surgically excluded (Sangi-Haghpeykar and Poindexter, 1995; Hemmings *et al.*, 2004).

The strength of our study lies in the following points: (i) the large number of severe forms of endometriosis (DIE, III and IV rAFS stages), (ii) the selection of cases and controls based on strict surgical and histological criteria, (iii) relying on a surgical classification, (iv) using clinical data prospectively collected by questionnaire prior to surgery on the various epidemiological variables, including those that may affect BMI and thus constitute confounding biases and (v) having controls who were all surgically explored for excluding possibly asymptomatic endometriosis.

Yet, in spite of the precautions taken, we concede that there are no ideal control groups for studying endometriosis (Holt and Weiss,

Table III Association between BMI and endometriosis on a population matched on age and smoking habits.

BMI	<18.5	18.5–21.9	22–24.9	≥25
All endometriosis	$n = 33$	$n = 126$	$n = 40$	$n = 39$
Univariate OR (95% CI)	3.4 (1.7–6.9)	2.9 (1.8–4.6)	Reference	1.3 (0.7–2.2)
Multivariate OR (95% CI)	3.3 (1.6–6.8)	2.7 (1.6–4.4)		1.2 (0.7–4.4)
DIE	$n = 15$	$n = 52$	$n = 17$	$n = 13$
Univariate OR (95% CI)	3.7 (1.6–8.8)	2.8 (1.5–5.2)	Reference	1 (0.4–2.0)
Multivariate OR (95% CI)	3.3 (1.3–8.8)	2.6 (1.3–5.5)		.8 (0.3–2.1)
OMA	$n = 12$	$n = 54$	$n = 18$	$n = 17$
Univariate OR (95% CI)	2.8 (1.12–6.9)	2.7 (1.5–5.1)	Reference	1.2 (0.6–2.6)
Multivariate OR (95% CI)	2.7 (1.1–6.1)	2.9 (1.5–5.4)		1.2 (0.6–2.6)

BMI, Body mass index; DIE, deep infiltrating endometriosis; OMA, ovarian endometrioma.
Multivariate analysis has been adjusted for gastro-intestinal and chronic pelvic pain symptoms VAS ≥ 7, parity and oral contraceptive use.
Women with a BMI ≥ 22 and <25 served as a reference population.

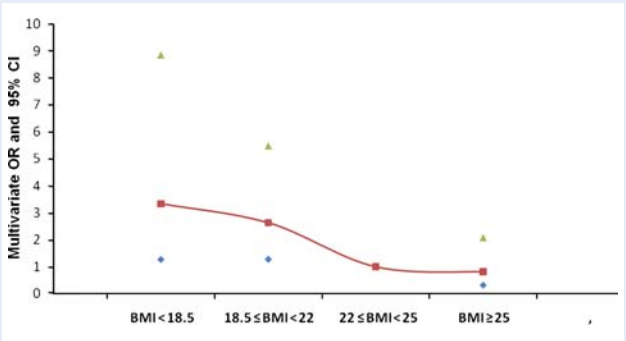

Figure 3 Association between BMI and the risk of DIE. Triangular point is 95% upper confidence limit of OR and Diamond point is 95% lower confidence limit of OR.

2000). The existence of biases is indeed always possible, a rule that also applies to our control group. In our study, biases might stem from the fact that all control patients had a benign gynecological ailment that motivated the surgical exploration, some possibly linked to higher BMIs (infertility, polycystic ovaries, etc.). For cases, our studied population selected at the time of surgery could differ from endometriosis patients not needing surgery. Patients who need surgery for either pain and/or infertility probably have more severe forms of the disease, which could magnify the difference with controls. Of note too is the fact that our study is underpowered to strictly exclude possible associations between SUP and low BMI. Finally, we concede that for cases and controls alike, the questionnaires albeit prospectively filled (before surgery) nonetheless banks on historical data and could thus be subject to recall biases. For example, height and weight are self-reported, but it is unlikely that errors differently affect cases and controls. Furthermore, it was shown (Engstrom *et al.*, 2003) that overweight patients tend to underestimate their weight, a factor that would minimize, not increase the difference observed.

The reason for BMI to be lower in endometriosis, particularly in DIE, is still unclear with no generally agreed scientific explanation. A widely accepted theory for the pathogenesis of endometriosis is that the disease stems from retrograde shedding of possibly altered endometrial cells and debris that attach and implant in various areas of the pelvic cavity. Different hypotheses have been proposed to account for the results of studies on nutritional (Parazzini *et al.*, 2004), hormonal (Zeitoun and Bulun, 1999), environmental (Louis *et al.*, 2005) and genetic factors (Zondervan *et al.*, 2002; Borghese *et al.*, 2008) predisposing to the disease. Hormonal and other characteristics of endometriotic cells may be involved; unlike normal endometrium, endometriotic lesions produce estrogen resulting in higher local estrogen concentrations (Zeitoun and Bulun, 1999), which favors the development of the disease (Lessey, 2000). Adipocytes are capable of both estrogen synthesis and inactivation; the latter could possibly prevent the growth and dissemination of endometriotic cells. Another hormonal system, leptin, has been shown to be impaired in case of both endometriosis and obesity. Leptin, an adipocyte-derived hormone found elevated in overweight patients in direct correlation with BMI (McGregor *et al.*, 1996), is also involved in the stimulation of reproductive functions (Kitawaki *et al.*, 2000). Patients with endometriosis were shown to have significantly higher peritoneal fluid leptin concentrations, a difference that remained significant when corrected for BMI (Matarese *et al.*, 2000; De Placido *et al.*, 2001; Alviggi *et al.*, 2009; Pandey *et al.*, 2010). Leptin has been shown to influence the formation of endometriosis by different pathways (Mahutte *et al.*, 2003; Milewski *et al.*, 2008; Styer *et al.*, 2008; Wu *et al.*, 2010). Finally, genetic factors that are linked to endometriosis could also affect the metabolic determinant of weight. Genes known to be aberrantly expressed at implantation and other times in the cycle are candidates for partaking in the establishment of the disease (aromatase, metalloproteinases, VEGF, etc.; Borghese *et al.*, 2008). It can be hypothesized therefore that genetic factors determining endometriosis could also impact on, or be associated with those impacting on, BMI (Moen, 1994; Ordovas, 2001). All these hypotheses need to be further probed for determining the pathogensis of the observed link between endometriosis and low BMI.

It remains however that our results strongly suggest the existence of a real inverse correlation between BMI and endometriosis risk. Indeed, not only did the OR retain its statistical significance after

adjustment for confounding variables, but it was shown to be very high for the most severe forms of endometriosis. Furthermore, the OR for endometriosis decreases when BMI increases even in the normal weight range. Finally, while few studies have looked at BMI in early childhood and adolescence in patients later diagnosed with endometriosis, most have found that endometriosis is associated with a lower BMI (Hediger *et al.*, 2005; Nagle *et al.*, 2009; Vitonis *et al.*, 2010) independent of the adult BMI. These latter results show that BMI is not only different at the time of surgery but much earlier in the patient's reproductive life, suggesting that the expression of this trait may be concomitant with the very onset of the endometriotic disease.

Conclusion

Our study showed a significant inverse association between endometriosis and BMI, with the multivariate OR analysis being particularly high for the most severe forms of endometriosis, such as notably DIE. This epidemiological observation is interesting for two primary reasons: (i) it may support some pathogenesis hypotheses on the development and growth of endometriosis lesions, (ii) it is a simple-to-use clinical parameter that, associated with other factors such as pain, may raise the awareness of endometriosis early on and thus, help an earlier diagnosis (Chapron *et al.*, 2011a,b) leading to less extensive surgery in young women.

Authors' roles

C.C. and M.C.L.P. conceived and designed the study. M.C.L.P., C.C., D.Z. and A.S. analysed and interpreted the data. C.C., D.Z. and M.C.L.P. wrote the manuscript. C.C., C.S., B.B., M.C.L.P., P.S., I.S. and A.S. contributed to data collection and/or performed surgical procedures. All the authors contributed to writing the manuscript. All the authors approved the final version of the manuscript.

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Conflict of interest

D.Z. owns equity interest in Ultrast Inc and served on advisory boards of IBSA and Fensup Pharmaceuticals.

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