# Endometriosis-related infertility: ovarian endometrioma *per se* is not associated with presentation for infertility

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**STUDY QUESTION:** Is there an association between the endometriosis phenotype and presentation with infertility?

**SUMMARY ANSWER:** In a population of operated patients with histologically proven endometriosis, ovarian endometrioma (OMA) *per se* is not associated with an increased risk of presentation with infertility, while previous surgery for endometriosis was identified as a risk factor for infertility.

**WHAT IS KNOWN ALREADY:** The increased prevalence of endometriosis among subfertile women indicates that endometriosis impairs reproduction for reasons that are not completely understood.

**STUDY DESIGN, SIZE, DURATION:** This was an observational, cross-sectional study using data prospectively collected in all non-pregnant patients aged between 18 and 42 years, who were surgically explored for benign gynaecological conditions at our institution between January 2004 and March 2013. For each patient, a standardized questionnaire was completed during a face-to-face interview conducted by the surgeon during the month preceding surgery.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Surgery was performed in 2208 patients, of which 2066 signed their informed consent. Of the 1059 women with a visual diagnosis of endometriosis, 870 had histologically proven endometriosis and complete treatment for their endometriotic lesions, including 307 who presented with infertility. Univariate analysis and multiple logistic regression analysis were performed to determine factors associated with infertility.

**MAIN RESULTS AND THE ROLE OF CHANCE:** The following variables were identified as risk factors for endometriosis-related infertility: age >32 years (odds ratio [OR] = 1.9; 95% confidence interval [CI]: 1.4–2.4), previous surgery for endometriosis (OR = 1.9; 95% CI: 1.3–2.2), as well as peritoneal superficial endometriosis (OR = 3.1; 95% CI: 1.9–4.9); Conversely, previous pregnancy was associated with a lower rate of infertility (OR = 0.7; 95% CI: 0.6–0.9 and OR = 0.6; 95% CI: 0.4–0.9, respectively). OMA is not selected as a significant risk factor for infertility.

**LIMITATIONS, REASON FOR CAUTION:** The selection of our study population was based on a surgical diagnosis. We cannot exclude that infertile women with OMA associated with a diminished ovarian reserve, as assessed during their infertility work-up, were referred less frequently to surgery and might therefore be underrepresented. In addition we cannot exclude that our group of infertile women present associated other causes of infertility.

**WIDER IMPLICATIONS OF THE FINDINGS:** Identification of risk and preventive factors of endometriosis-related infertility can help improve clinical and surgical management of endometriosis in the setting of infertility.

# Introduction

Endometriosis, defined as the development of ectopic endometrium-like tissue outside of the uterine cavity (Sampson, 1927), is a common chronic gynaecologic disorder of still unknown origin that affects up to 10% of women of child-bearing age (Giudice, 2010). Being associated with persistent pelvic pain (Fauconnier and Chapron, 2005) and/or infertility (de Ziegler *et al.*, 2010), endometriosis poses significant public health problem. It not only affects health, well-being and quality of life of patients, but has also great impacts on daily life, work absenteeism and health care consumption (Fourquet *et al.*, 2010; Nnoaham *et al.*, 2011).

The severity of endometriosis is graded according to the location, the extent and the depth of penetration of the lesions (Dubuisson and Chapron, 1994). Three different endometriosis phenotypes can be distinguished, according to whether the endometriotic lesions remain located on the peritoneal surface (superficial peritoneal endometriosis [SUP]), give rise to ovarian cysts (ovarian endometrioma [OMA]) or invade the surrounding organs beneath the peritoneum such as the bladder, the vagina, the ureter, or the rectum (deep infiltrating endometriosis [DIE]).

While there are well-established relationships between the anatomical location of endometriotic lesions and pain (Fauconnier *et al.*, 2002; Vercellini *et al.*, 2007; Brawn *et al.*, 2014; Morotti *et al.*, 2014), the link between endometriosis and infertility is less well defined. Several mechanisms have been proposed to explain endometriosis-related infertility, including inflammation, distorted pelvic anatomy, endocrine and ovulatory abnormalities, peritoneal dysfunction, and altered hormonal and cell-mediated functions in the endometrium (de Ziegler *et al.*, 2010; Vercellini *et al.*, 2014a). However, the relationship between the endometriosis phenotype and infertility is far from clear.

The main objective of the present study was to analyse the association between patient characteristics, endometriotic lesion location, disease stage, endometriosis phenotype and presentation for infertility in a large group of women with histologically proven endometriosis.

# Materials and Methods

## Study design

This was an observational, cross-sectional study using data from a prospective database, the structure of which has already been detailed and published elsewhere (Chapron *et al.*, 2011b). Signed informed written consent was obtained from all included patients. The local Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) at our institution approved the study protocol.

## Study population

The database consisted of data from all non-pregnant patients aged less than 42 years, who underwent gynaecological surgery by laparotomy or laparoscopy from January 2004 to March 2013 at our institution. Excluded from this population were women with cancer, infectious disease and/or who refused to give their consent for participating in 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 dysmenorrhoea 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, etc.

For the purpose of this study, patients were selected based on histological and surgical criteria: patients with no visual lesion of endometriosis at surgery as well as patients visually diagnosed with endometriosis but without histological confirmation (Chapron *et al.*, 2010b), or patients who did not have, according to the surgeons' findings, a complete excision of endometriotic lesions (Lafay Pillet *et al.*, 2012), were excluded from the study. The resulting study population, i.e. patients with complete surgical removal of histologically proven endometriotic lesions, was divided into two groups according to whether they presented with infertility (study group) or not (control group).

Histologically proven endometriotic lesions were classified into three phenotypes: SUP, OMA and DIE. Because these three endometriotic phenotypes can be associated, patients were classified according to their worst lesion, that is, from least to most severe: SUP, OMA and DIE (Chapron *et al.*, 2011a). DIE was histologically defined as endometriotic lesions that infiltrate the *muscularis propria* (bladder, intestine, intrinsic ureter) after radical surgery (partial cystectomy, bowel resection, ureteral resection) (Chapron *et al.*, 2010a). For the other locations (uterosacral ligament(s), vagina, extrinsic ureter), DIE was arbitrarily defined as endometriotic tissue infiltrating beneath the peritoneum surface deeper than 5 mm (Koninckx and Martin, 1992). DIE lesions were classified according to five locations: bladder, uterosacral ligament(s), vagina, intestine and ureter (Chapron *et al.*, 2006). In cases of multiples DIE lesions, patients were classified according to the worst finding (least to most severe: uterosacral ligament(s), vagina, bladder, intestine and ureter) (Chapron *et al.*, 2006). During the surgical procedure, the extent of endometriosis (stages and mean scores: total, adhesions, implants) was assessed according to the American Society for Reproductive Medicine (ASRM) classification (ASRM, 1997).

## Data collection

For each patient, data were collected in face-to-face interviews conducted by the surgeon during the month preceding surgery using standardized questionnaire, as previously described (Chapron *et al.*, 2010b). The questionnaire queried about general data (age, body mass index [BMI], family history, surgical history, obstetrical history, smoking habits, oral contraceptive pill [OCP] use), gynaecological data (characteristics about the menstrual cycle and menstruations, existence of dysmenorrhoea, existence and duration of infertility), and history of symptoms and treatment during adolescence (age at menarche, primary dysmenorrhoea and its consequences on life [e.g. absenteeism from school], prescription of OCP to treat severe primary dysmenorrhoea).

## Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD) or number (percent) of subjects for continuous and categorical variables, respectively. A stepwise

multiple logistic regression was conducted to determine factors associated with infertility. First, between-group comparisons were performed using the Student's t-test or Pearson's $\chi^2$ test as appropriate. Crude odds ratios (OR) with 95% confidence intervals (CI) were then estimated separately for each variable associated with infertility at a threshold of $P < 0.10$ in the previous univariate analysis. We then run a multiple logistic regression including six variables with a P-value less than 0.005. A stepwise ascendant selection by likelihood ratio test has been run on 4 steps selecting 4 variables with a significant adjusted OR for infertility ($P < 0.001$). After Bonferroni correction for multiple comparisons we still have an α value at 0.05 level. Statistical significance was considered at $P < 0.05$. Statistical analysis was performed using the SPSS software version 18.0.0 (SPSS Inc., Chicago, IL, USA).

# Results

From January 2004 to March 2013, 2066 women underwent gynaecological surgery at our institution and gave their informed consent for participating in the study (Fig. 1). Of these 2066 women, 1059 (51.3%) were visually diagnosed with endometriosis. The resulting patient population consisted of the 870 patients for whom endometriosis diagnosis had been histologically confirmed and complete excision of endometriotic lesions had been performed (Fig. 1). For these patients, indications for surgery were the following: painful symptoms without associated infertility (563 patients, 64.7%), pain associated to infertility (223 patients, 25.6%) and isolated infertility without pain (84 patients, 9.7%). Demographic and clinical characteristics of these 870 patients are presented in Table I. About one-third of patients (332 cases, 38.2%) had previous surgery for endometriosis, including OMA surgery for 147 patients (16.9%). Patient's distribution according to their worst endometriotic phenotype was as follows: SUP (147 patients, 16.9%), OMA (229 patients, 26.3%), and DIE (494 patients, 56.8%). Of 494 DIE patients, 183 (37.0%) presented associated OMA (right 43, left 79 and bilateral 61). Thus, a total of 412 patients (47.4%) presented OMA. Data for
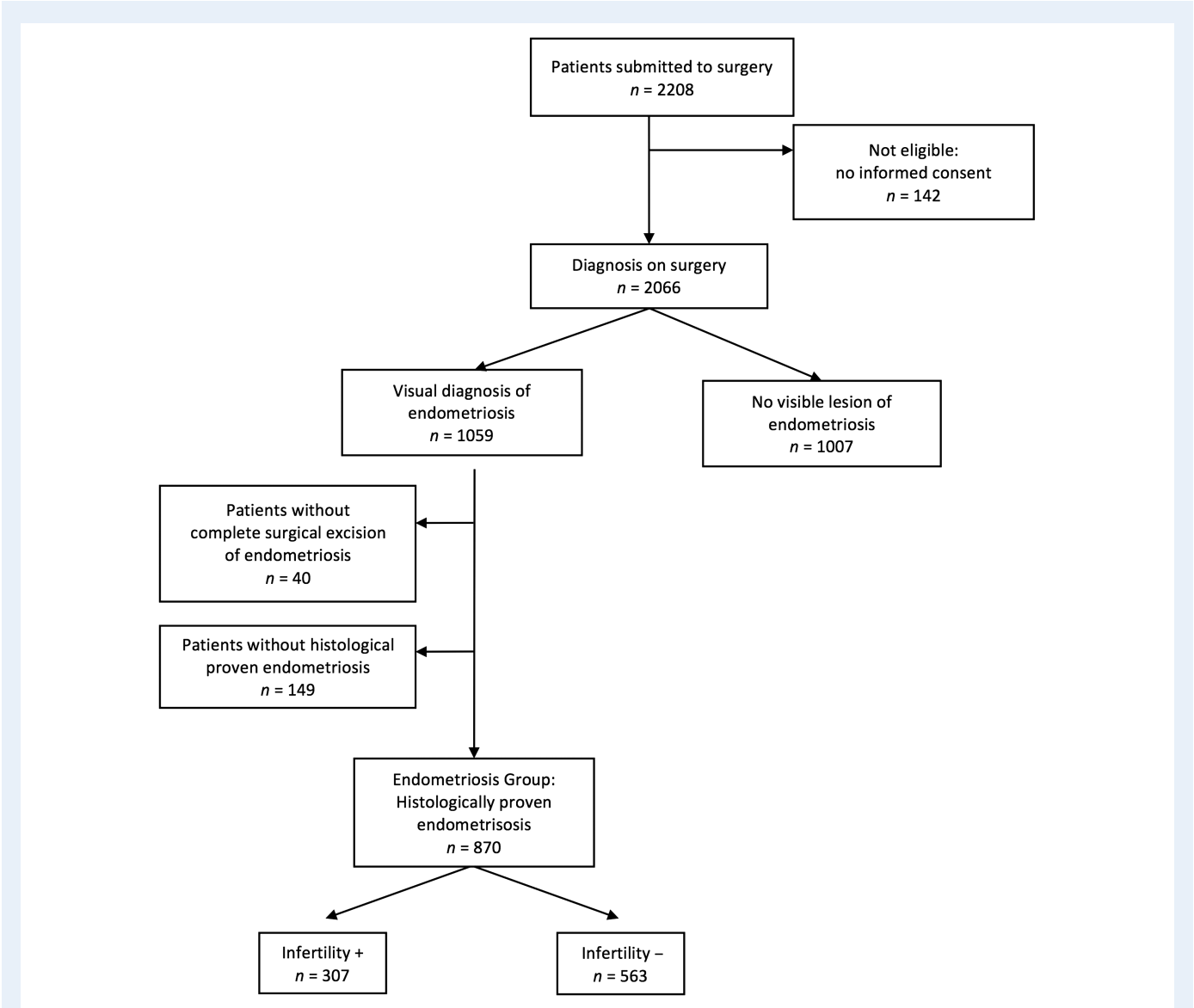


**Figure 1** Patients inclusion flowchart.

**Table I** Baseline characteristics of endometriotic patients according to history of presentation for infertility.[a]

| Variable | All patients (n = 870) | Infertility+ (n = 307) | Infertility− (n = 563) | P |
|---|---|---|---|---|
| Age (years) | 31.7 ± 5.3 | 32.5 ± 4.0 | 31.3 ± 5.9 | 0.001[e] |
| Height (cm) | 165.2 ± 6.3 | 165.1 ± 6.6 | 165.0 ± 7.1 | 0.849[e] |
| Weight (kg) | 60.1 ± 10.4 | 59.8 ± 10.2 | 60.2 ± 10.5 | 0.607[e] |
| Body mass index (kg/m$^2$) | 22.0 ± 3.6 | 21.9 ± 3.5 | 22.2 ± 4.3 | 0.378[e] |
| Nulligravida | 585 (67.3%) | 220 (71.7%) | 60 (10.7%) | <0.001[f] |
| Smoking habits | 390 (44.8%) | 136 (44.3%) | 254 (45.2%) | 0.62[f] |
| Familial history of endometriosis | 102 (11.7%) | 28 (9.1%) | 74 (13.1%) | 0.08[f] |
| Absenteeism from school during menstruation | 276 (31.7%) | 103 (33.6%) | 173 (30.7%) | 0.39[f] |
| Prescription of OCP for severe primary dysmenorrhoea | 183 (21.0%) | 73 (23.8%) | 109 (19.4%) | 0.13[f] |
| Previous history of surgery for endometriosis | | | | |
|     Endometriosis surgery | 332 (38.2%) | 137 (44.6%) | 195 (34.7%) | 0.004[f] |
|     Endometrioma surgery | 147 (16.9%) | 62 (20.2%) | 85 (15.1%) | 0.063[f] |
| Previous OCP use | | | | <0.001[f] |
|     Never user | 95 (10.9%) | 30 (9.8%) | 65 (11.5%) | |
|     Ever user | 576 (66.2%) | 253 (82.4%) | 323 (57.4%) | |
|     Current user | 199 (22.9%) | 24 (7.8%) | 175 (31.1%) | |
| Mean ASRM implants score[b] | 15.0 ± 12.5 | 16.0 ± 13.5 | 14.5 ± 11.9 | 0.105[e] |
| Mean ASRM adhesions score[b] | 20.3 ± 24.3 | 24.2 ± 26.2 | 18.1 ± 22.8 | 0.001[e] |
| Mean ASRM total score[b] | 35.1 ± 31.4 | 40.2 ± 34.4 | 32.6 ± 29.7 | 0.001[e] |
| ASRM stage[b] | | | | <0.001[f] |
|     I | 155 (17.8%) | 59 (19.2%) | 96 (17.1%) | |
|     II | 176 (20.2%) | 52 (16.9%) | 124 (22.0%) | |
|     III | 223 (25.6%) | 59 (19.2%) | 164 (29.1%) | |
|     IV | 316 (36.4%) | 137 (44.6%) | 179 (31.8%) | |
| Peritoneal superficial endometriosis (SUP) | 147 (16.9%) | 70 (22.8%) | 77 (13.7%) | <0.001[f] |
| Ovarian endometrioma isolated (OMA) | 229 (26.3%) | 65 (21.2%) | 164 (29.1%) | |
| Deeply infiltrating endometriosis (DIE)[c] | 494 (56.8%) | 172 (56.0%) | 322 (57.2%) | |
|     With OMA | 183 (37.0%) | 85 (27.7%) | 98 (17.4%) | |
|     Without OMA | 311 (73.0%) | 87 (28.3%) | 224 (39.8%) | |
| Mean number of DIE lesions | 2.8 ± 1.9 | 3.2 ± 2 | 2.7 ± 1.8 | 0.004[e] |
| Total number of DIE lesions | | | | 0.041[f] |
|     I | 150 (30.1%) | 43 (25.0%) | 107 (33.2%) | |
|     2 | 115 (23.4%) | 34 (19.8%) | 81 (25.1%) | |
|     ≥3 | 229 (46.5%) | 95 (55.2%) | 134 (41.7%) | |
| Anatomical distribution of DIE[c,d] | | | | |
|     USL | 343 (69.6%) | 117 (38.1%) | 225 (40.0%) | 0.579[f] |
|     Vagina | 216 (43.8%) | 82 (26.7%) | 134 (23.8%) | 0.350[f] |
|     Bladder | 83 (16.8%) | 26 (8.5%) | 57 (10.1%) | 0.423[f] |
|     Intestine | 288 (58.4%) | 115 (37.5%) | 172 (30.6%) | 0.039[f] |
|     Ureter | 42 (8.5%) | 8 (2.6%) | 34 (6.0%) | 0.024[f] |
| Worst DIE lesion[c] | | | | 0.009[f] |
|     USL | 115 (23.4%) | 36 (21%) | 79 (24.5%) | |
|     Vagina | 40 (8.1%) | 8 (4.6%) | 32 (10%) | |
|     Bladder | 42 (8.5%) | 12 (7%) | 30 (9.4%) | |
|     Intestine | 254 (51.5%) | 108 (62.8%) | 147 (45.6%) | |
|     Ureter | 42 (8.5%) | 8 (4.6%) | 34 (10.5%) | |

*Continued*

**Table I** *Continued*

| Variable | All patients (*n* = 870) | Infertility+ (*n* = 307) | Infertility− (*n* = 563) | P |
|---|---|---|---|---|
| Endometrioma size (cm) | | | | |
| Right | 4.1 ± 2.5 | 3.7 ± 2.6 | 4.1 ± 2.5 | 0.263[e] |
| Left | 4.1 ± 3.0 | 4.2 ± 3.1 | 4.4 ± 3.0 | 0.647[e] |

DIE, deeply infiltrating endometriosis; OCP, oral contraceptive pill; OMA, ovarian endometrioma; ASRM, American Society for Reproductive Medicine classification; USL, uterosacral ligaments.

[a]Data reported as mean ± standard deviation or number (%).
[b]Score according to the American Society for Reproductive Medicine classification (ASRM, 1997).
[c]According to surgical classification for DIE (Chapron *et al.*, 2006).
[d]Sometimes more than one for the same patient.
[e]Student's *t*-test.
[f]Pearson's $\chi^2$ test.

ASRM stage, mean total, adhesions and implants scores, anatomical distribution of DIE lesions, and classification according to the worst DIE lesions are also presented in Table I.

Endometriosis was associated with presentation for infertility in 307 patients (35.3%). Demographic and clinical characteristics of endometriotic patients presenting (study group: *n* = 307; 35.3%) or not (control group: *n* = 563; 64.7%) with infertility are detailed in Table I. BMI, smoking habits, family history of endometriosis, absenteeism from school during menstruation, OCP use to treat severe primary dysmenorrhoea, and mean ASRM implants score were comparable between the two groups. Conversely, significant between-group differences were observed in age, gravidity, previous surgery for endometriosis, mean ASRM adhesions and total scores, ASRM stage, as well as extent of DIE lesions (mean and total number of DIE lesions). Compared with the control group, infertile patients presented more frequently SUP lesions (22.8% [70 patients] versus 13.7% [77 patients]; *P* < 0.001), while prevalence of DIE was similar between the two groups (56.0% [172 patients] versus 57.2% [322 patients]; *P* = ns). However, anatomical distribution of DIE lesions was more severe in the infertile group, with a significantly higher involvement of the intestine (37.5% [115 patients] versus 30.6% [172 patients]; *P* = 0.039). In addition, intestinal DIE lesion was significantly more frequently observed as the worst DIE lesion in the infertile group (62.8% [108 patients] versus 45.6% [147 patients]; *P* = 0.009).

Results of the multivariate analysis demonstrated that risk factors associated with the increased likelihood of presentation for infertility included age >32 years, SUP endometriosis phenotype, and previous surgery for endometriosis. On the contrary, previous pregnancy (gravidity >0) appeared as protective factors, in that it is associated with a lower rate of infertility (Table II). OMA is not selected as a significant risk factor for infertility.

Within the population of 412 OMA patients, OMA was associated with presentation for infertility in 150 patients (36.4%). Demographic and clinical characteristics of OMA patients presenting (study group: *n* = 150; 36.4%) or not (control group: *n* = 262; 63.6%) with infertility are presented in Table III. Age, BMI, gravidity, smoking habits, and OMA size were comparable between the two groups. Conversely, significant between-group differences were observed in previous surgery for endometriosis, ASRM scores and stage, as well as extent of endometriotic lesions. Compared with the control group, OMA was more frequently associated with DIE in infertile patients (56.7% [85 patients] versus 37.4% [98 patients]; *P* < 0.001). In addition, anatomical

distribution of DIE lesions was more severe in the infertile group, with significantly more intestinal location as worst DIE lesion (45.3% [68 patients] versus 26% [68 patients]; *P* < 0.001).

# Discussion

This cross-sectional study, using a large hospital-based series of patients with histologically proven endometriosis, found that age, previous surgery for endometriosis, as well as SUP endometriosis phenotype, were significant risk factors for presentation for endometriosis-related infertility. Conversely, previous pregnancy was significantly associated with lower rate of infertility. After multivariate analysis OMA is not selected as a significant risk factor for presentation for infertility. For patients presenting with OMA-related infertility, OMA was more frequently associated with DIE, and particularly with the most severe form of DIE that involves intestinal lesions.

The strength of this study lays in the following points: (i) the patients were selected based on the fact that they were planned for surgery and not only according to the presence of infertility; (ii) the large number of endometriotic patients enrolled (870 women, including 307 with endometriosis-related infertility); (iii) all the patients were surgically explored and endometriosis was always histologically proven; and (iv) the analysis of the results according to endometriosis phenotypes (SUP, OMA, DIE).

Selection biases may have occurred, however, because recruitment was performed at a single centre, which is specialized in the care of severe endometriosis (DIE). This may contribute to an elevated rate of patients affected by severe forms of endometriosis and/or presenting with infertility. In addition, our study included women for whom surgery was decided, we can therefore not exclude that infertile women with OMA associated with a diminished ovarian reserve, as assessed during their infertility work-up, were referred less frequently to surgery and might therefore be underrepresented. In addition we cannot exclude the existence of potential associated other causes of infertility in our group of infertile endometriosis affected women. Finally, numerous epidemiological variables were prospectively collected using questionnaires before surgery, which may constitute potential confounding factors.

Our findings have clinical implications that are of prime importance in daily practice. The fact that, in a population of operated patients with histologically proven endometriosis, OMA *per se* is not associated with an increased risk of presentation for infertility should indeed be considered when choosing the best treatment of OMA in women desiring to

**Table II** Factors associated with presentation for infertility—multiple logistic regression model.

| Variable | OR (95% CI) | P |
|---|---|---|
| Age >32 years[a] | 1.9 (1.4–2.5) | <0.001 |
| Gravidity >0 | 0.7 (0.6–0.9) | <0.001 |
| Peritoneal superficial endometriosis | 3.1 (1.9–4.9) | <0.001 |
| Previous history of surgery for endometriosis | 1.9 (1.3–2.2) | <0.001 |

CI, confidence interval; OR, odds ratio; ASRM: American Society for Reproductive Medicine classification.
[a]Binary variable >32 versus ≤32 years.

conceive. The general consensus is that OMA larger than 4 cm should be surgically removed (Dunselman et al., 2014), both to reduce pain and to improve spontaneous conception rates. However, two important questions should be answered before proceeding with surgery: first, is there a relationship between OMA and infertility? and second, what are the risks associated with OMA surgical procedures on subsequent fertility?

Firstly, the impact of OMA per se on ovarian reserve and fertility is controversial. While it has been suggested that the presence of OMA per se is associated with a reduction in ovarian reserve (Maneschi et al., 1993; Uncu et al., 2013; Sanchez et al., 2014), this has been contradicted by numerous findings. In a recent study conducted in 244 women with unilateral OMA, ovulation was monitored during 6 cycles using transvaginal ultrasonography and compared between the affected and healthy ovary. Results showed that OMA does not negatively impact rate of spontaneous ovulation in the affected ovary (Maggiore et al., 2015). These results were affected neither by the laterality, number and size of OMA nor with associated DIE diagnosed using transvaginal ultrasonography. During the 6-month study period, 105 patients spontaneously conceived (43.0%; 95% CI: 36.7–49.5%) (Maggiore et al., 2015). These results are in agreement with those from Streuli et al., who demonstrated, in a large cohort of 726 patients (313 histologically proven endometriosis and 412 controls), that endometriosis and OMA per se (including cases with uni- or bilateral OMA) do not result in lower anti-Müllerian hormone (AMH) levels (Streuli et al., 2012). Ferrero et al. demonstrated that OMA recurrence per se did not have a significant effect on ovarian reserve markers (Ferrero et al., 2015). Consistently, results of our study suggest that OMA is not associated with an increased risk of infertility, infertility rate being similar in both overall endometriotic and OMA populations (35.3% (307/870) and 36.4% 150/412), respectively). As regards women undergoing assisted reproductive technologies (ART), it has been shown that, in cases of women with unilateral OMA, ovarian responsiveness to hyperstimulation was the same between the affected and intact ovary (Somigliana et al., 2015). In cases of unoperated bilateral OMA, although the responsiveness to hyperstimulation was significantly reduced, the quality of the oocytes retrieved and the chances of pregnancy were not affected (Benaglia et al., 2013). No between-group difference in in vitro fertilization (IVF) outcomes (clinical pregnancy rates per cycle, peak serum estradiol levels, number of oocytes retrieved, number of gonadotrophins ampoules required and number of embryos available for transfer) was observed in patients who underwent, or not, surgical treatment of OMA before IVF (Tsoumpou et al., 2009). Similarly, removing OMA before IVF did not improve the chance of pregnancy (Garcia-Velasco et al., 2004). Finally, after a surgical OMA excision,

IVF cycles outcomes were not affected by an OMA recurrence (Somigliana et al., 2011).

Secondly, numerous data have demonstrated that laparoscopic stripping of OMA damages the ovarian reserve (Benaglia et al., 2010; Raffi et al., 2012; Somigliana et al., 2012) due to inadvertent removal of healthy tissue in addition to the OMA wall (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2002, 2005, 2007). This has also been confirmed by Streuli et al., who showed that, for endometriotic patients, AMH levels were decreased only in women with previous OMA surgery, independently of the presence of current OMA (Streuli et al., 2012). The negative impact of OMA surgery on the ovarian reserve is correlated to: (i) patient's age (Alborzi et al., 2014); (ii) OMA size (Roman et al., 2010; Coccia et al., 2011; Tang et al., 2013); (iii) bilateral OMA (Busacca et al., 2006; Esinler et al., 2006; Coccia et al., 2011); (iv) inexperienced surgeon (Yu et al., 2010; Muzii et al., 2011); and (v) repetitive surgery for OMA recurrence (Ferrero et al., 2015; Muzii et al., 2015). Regarding patients undergoing ART, IVF outcome was significantly impaired in women previously operated for bilateral OMA (Esinler et al., 2006; Somigliana et al., 2008). Finally live birth rate after IVF was lower in women with a diminished ovarian reserve (DOR) diagnosed after a previous OMA surgery compared with women with idiopathic DOR (Roustan et al., 2015).

All together these observations tend to indicate that OMA-related infertility, and especially the deleterious effects on ovarian reserve, may be more related to surgical treatment of OMA rather than to OMA per se. These are important considerations to be taken into account for the management of OMA in the setting of infertility given that: (i) there is a high risk of OMA recurrence after laparoscopic excision (Busacca et al., 1999; Koga et al., 2006; Guo, 2009); (ii) reproductive performance are significantly lower after repetitive versus primary surgery for both women seeking conception and infertile women (Vercellini et al., 2009); (iii) repetitive surgery for endometriosis recurrence does not increased the chance of pregnancy compared with ART (Pagidas et al., 1996; Cheewadhanaraks et al., 2004); (iv) endometriosis surgery before IVF does not increase the fertility results (Demirol et al., 2006); (v) risks of conservative management of OMA (OMA infection, follicular fluid contamination with endometrioma, pregnancy complications risk, and cancer development later in life) does not support the systematic necessity of surgery before ART, specifically in women with small OMA (Somigliana et al., 2015); and (vi) delaying attempts to conceive after surgery for endometriosis is associated with a lower pregnancy rate and a higher risk of recurrence (Somigliana et al., 2010). On the basis of all these findings, the decision to remove or not an OMA in the setting of infertility must be carefully considered.

From our point of view, laparoscopic intraperitoneal cystectomy, which is considered as the gold standard for OMA treatment (Chapron et al., 2002; Hart et al., 2005; Kennedy et al., 2005), should not be automatically performed. OMA management should be individualized and should be made on a case-by-case basis, taking into account the following parameters: patient's desire; ovarian reserve (AMH levels and antral follicule count); uni- or bilateral OMA; patient's age; existence and duration of infertility; immediate or delayed desire for pregnancy; associated infertility factors (tubal, sperm,...); associated DIE and/or adenomyosis; previous surgery for endometriosis, and specifically previous OMA surgery; existence and intensity of associated pelvic pain. Especially, in the case of unilateral OMA in patients without history of infertility desiring to conceive, surgery is not required

**Table III** Baseline characteristics of ovarian endometrioma (OMA) patients according to history of presentation for infertility.[a]

| Variable | Infertility+ (n = 150) | Infertility− (n = 262) | P |
|---|---|---|---|
| Age (years) | 32.5 ± 3.8 | 31.6 ± 5.8 | 0.053[e] |
| Height (cm) | 164.6 ± 6.6 | 165.7 ± 8.2 | 0.171[e] |
| Weight (kg) | 60.7 ± 10.6 | 60.7 ± 10.9 | 0.946[e] |
| Body mass index (kg/m$^2$) | 22.4 ± 3.7 | 22.2 ± 5.0 | 0.703[e] |
| Nulligravida | 116 (77.3%) | 184 (70.2%) | 0.119[f] |
| Smoking habits | 67 (44.7%) | 117 (44.7%) | 0.998[f] |
| Previous history of surgery for endometriosis | | | |
|     Endometriosis surgery | 76 (50.7%) | 80 (30.7%) | <0.001[f] |
|     Endometrioma surgery | 39 (26.0%) | 55 (21.3%) | 0.279[f] |
| Mean ASRM implants score[b] | 27.6 ± 10.1 | 25.0 ± 9.1 | 0.012[e] |
| Mean ASRM adhesions score[b] | 33.1 ± 25.4 | 24.5 ± 24.2 | 0.001[e] |
| Mean ASRM total score[b] | 60.7 ± 30.5 | 49.5 ± 28.9 | <0.001[e] |
| ASRM stage[b] | | | <0.001[f] |
|     II | 0 (0%) | 1 (0.4%) | |
|     III | 50 (33.3%) | 138 (52.7%) | |
|     IV | 100 (66.7%) | 123 (46.9%) | |
| Deeply infiltrating endometriosis (DIE)[c] | 85 (56.7%) | 98 (37.4%) | <0.001[f] |
| Mean number of DIE lesions | 3.8 ± 2.0 | 3.4 ± 1.9 | 0.162[e] |
| Total number of DIE lesions | | | <0.001[f] |
|     1 | 10 (11.8%) | 19 (19.4%) | |
|     2 | 17 (20.0%) | 21 (21.4%) | |
|     ≥3 | 58 (68.2%) | 58 (59.2%) | |
| Anatomical distribution of DIE[c,d] | | | 0.294[f] |
|     USL | 57 (38.0%) | 69 (26.3%) | 0.013[f] |
|     Vagina | 50 (33.3%) | 48 (18.3%) | 0.001[f] |
|     Bladder | 8 (5.3%) | 12 (4.6%) | 0.732[f] |
|     Intestine | 68 (45.3%) | 68 (26%) | <0.001[f] |
|     Ureter | 5 (3.3%) | 14 (5.3%) | 0.349[f] |
| Worst DIE lesion[c] | | | <0.001[f] |
|     USL | 10 (11.8%) | 20 (20.4%) | |
|     Vagina | 5 (5.9%) | 6 (6.1%) | |
|     Bladder | 1 (1.2%) | 3 (3.1%) | |
|     Intestine | 64 (75.3%) | 56 (57.1%) | |
|     Ureter | 5 (5.8%) | 14 (13.3%) | |
| Endometrioma size (cm) | | | |
|     Right | 3.7 ± 2.6 | 4.1 ± 2.5 | 0.303[e] |
|     Left | 4.2 ± 3.1 | 4.4 ± 3.0 | 0.628[e] |

DIE, deeply infiltrating endometriosis; ASRM, American Society for Reproductive Medicine classification; USL, uterosacral ligaments.
[a]Data reported as mean ± standard deviation or number (%).
[b]Score according to the American Society for Reproductive Medicine classification (ASRM, 1997).
[c]According to surgical classification for DIE (Chapron et al., 2006).
[d]Sometimes more than one for the same patient.
[e]Student's t-test.
[f]Pearson's $\chi^2$ test.

immediately because of the good short-term pregnancy rates despite the presence of OMA (Maggiore et al., 2015). For the other cases, three therapeutic strategies may be proposed depending on the clinical patient's situation (Fig. 2).

(a) The first category of patients (group A according to Fig. 2) consists of women presenting with OMA-related infertility without pelvic pain. In these patients, and because of the desire to conceive, hormonal medical treatment is contraindicated. Alternative treatments
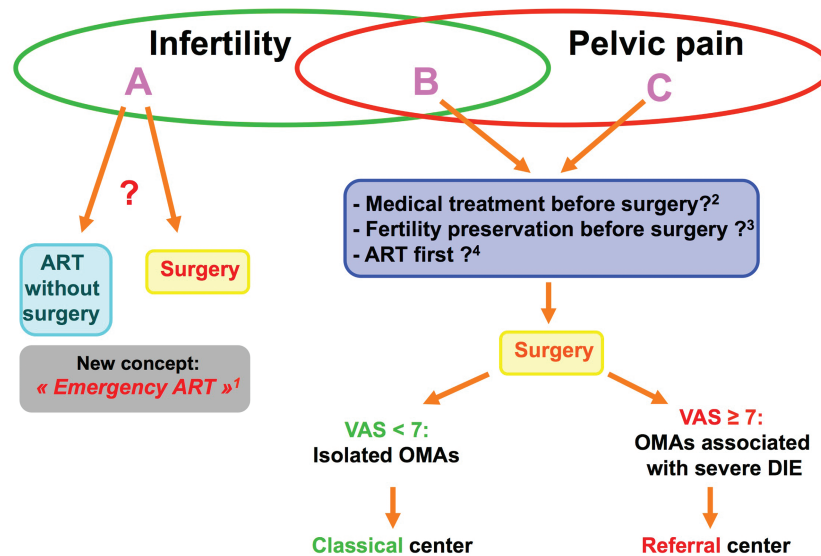
**Figure 2** Ovarian endometrioma: modern management. [1]In case of altered ovarian reserve, advanced age, longlasting infertility or in case of semen characteristics or tubal status that are incompatible with natural conception, direct ART should be envisioned (de Ziegler et al., 2010). [2]Antigonadotropic medical treatment may allow an expectant management in order to planned surgery in the best moment of endometriosis women life to avoid repetitive surgery (Sibiude et al., 2014). [3]Given the existence of a clear risk of ovarian reserve damage after surgery, fertility preservation procedures should be proposed to patients who don't present with infertility or with no current desire to conceive (Somigliana et al., 2015). [4]ART can be considered as a first-line option with satisfactory results in term of pregnancy (Ballester et al., 2012). ART: assisted reproductive technologies; DIE: deep infiltrating endometriosis; OMA: ovarian endometrioma; VAS: visual analogue scale.

include ART and surgery. ART should be proposed in the following cases: older patients, altered ovarian reserve, previous surgery for endometriosis, existence of associated infertility factors (male, tubal pathology,...), bilateral OMA. In patients with ovarian damage, surgery must be absolutely avoided as it may further lower the patient's ovarian reserve. In these cases, an 'emergency ART' should be envisioned, whatever the patient's age (de Ziegler et al., 2010).

(b) The second category of patients (group C according to Fig. 2) consists of women presenting with OMA-associated pelvic pain without infertility or with no current desire to conceive. In these patients, hormonal medical treatment should be considered as the first-line therapeutic option, provided that there is no contra-indication (Ferrero et al., 2015). First-line treatment should consist of OCPs and progestogens. In case of treatment failure and/or if the treatment is not tolerated, gonadotrophin-releasing hormone (GnRH) agonists with add-back therapy may be considered as second-line therapeutic option (Descamps et al., 2014). Medical treatment should be preferred as long as it allows proper management of endometriosis, provided that a regular clinical and radiological follow-up of OMA is performed. If medical treatment fails to provide adequate pain relief, surgical treatment should be envisioned. However, it has been suggested that, in those patients with 'painful OMA', the OMA per se may not be the endometriotic lesion that is directly involved in the pathogenesis of pain generation. Khan et al. showed that, in women with OMA, pelvic pain was usually associated with superficial endometriosis, which is responsible of inflammatory reaction with elevated prostaglandin production and contributes to the generation of pain (Kahn et al., 2013). Similarly, Chapron et al. reported

that, in case of OMA, severe pelvic pain was significantly associated with DIE (Chapron et al., 2012). While surgical treatment of SUP is quite easy to perform, it is not the case for DIE, where complete removal of all the lesions is required for effective pain management. Given the fact that OMA was shown to be a marker for greater severity for DIE (Redwine, 1999; Chapron et al., 2009), 'painful OMA' must be considered as 'synonymous of severe DIE' with multifocal lesions and intestinal/and or ureteral involvement (Chapron et al., 2009). Surgical management of such cases requires both a thorough preoperative radiological assessment with comprehensive cartography of DIE lesions as well as a multidisciplinary operative team (involving gynaecologist, intestinal and urologist surgeons) in a reference centre dedicated to the treatment of severe endometriosis (Sibiude et al., 2014). Of note, persistence of endometriotic lesions due to an incomplete initial surgical procedure currently leads to many misleading diagnosis of endometriosis recurrence (Sibiude et al., 2014). The worst approach, for patients with 'painful OMA', would consist of a surgical excision of OMA without removal of associated DIE lesions, as it would expose the patient to the risk of iterative surgery, and thus to a cumulative risk of decrease in ovarian reserve, without providing pain relief. Furthermore, given the potentially deleterious effect of surgery on subsequent fertility, fertility preservation procedures should be proposed to patients who don't present with infertility or with no current desire to conceive (Garcia-Velasco et al., 2013; Somigliana et al., 2015).

(c) Lastly, the third category of patients (group B according to Fig. 2) consists of women presenting with OMA-related infertility and pelvic pain. In these patients, therapeutic options include ART and

surgery. ART should be preferred in the same situations than those described for the first category of patients (group A). In the other cases, surgery should be performed as described for the second category of patients (group C). For patients who refuse surgical treatment, and/or who are not too painful, and/or who give priority to their desire to conceive, ART could be considered as a first-line option with satisfactory results in term of pregnancy (Ballester et al., 2012). This therapeutic strategy may be of particular interest for patients with adenomyosis associated with endometriosis (Kunz et al., 2005; Naftalin et al., 2012). Adenomyosis can cause uterine bleeding (Naftalin et al., 2014) and pelvic pain (Lazzeri et al., 2014), and constitutes an important factor of infertility (Kunz et al., 2005; Vercellini et al., 2014b). In these patients, an uterine conservative DIE surgery (i.e. a surgical excision of endometriosis without hysterectomy due to the desire to conceive) would expose the patient to a high-risk and complicated surgical procedure without guaranteeing satisfactory improvement of pain and/or menorrhagia (Parker et al., 2006; Ferrero et al., 2009; Lazzeri et al., 2014). Administration of post-ART hormonal medical treatment would allow scheduling of a single surgical intervention to perform complete removal of all the lesions (OMA, DIE and associated adenomyosis).

Overall, the objectives of these proposed strategies are: (i) first, to avoid unnecessary surgical procedures, and especially those contributing to damage ovarian reserve; and (ii) second to perform 'the endometriosis surgery' at the appropriate time. Ideally, patients should undergo surgical treatment only once in their 'endometriosis life'. In particular, use of hormonal medical treatment in patients with no immediate desire to conceive (with or without infertility) allows delaying the surgical intervention at the best time. Similarly, the place of ART in the treatment sequence should be carefully considered. Currently, ART is too often proposed at the end of the 'infertility story' after several surgical procedures, especially for OMA management. A main objective for the future would be to identify those patients for whom there are benefits to perform ART first, before the surgery.

In conclusion, our study demonstrates, in a population of operated patients with histologically proven endometriosis, that OMA per se has no negative impact on fertility. This has to be taken into account in daily clinical practice for the management of OMA in the setting of infertility. The general consensus considering that operative laparoscopy with OMA cyst excision represents automatically the first-line treatment needs to be revisited.

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## Authors' roles

C.C. is the coordinator of the project. C.C. and P.S. conceived and designed the study. M.C.L., L.M., V.G., P.M., B.B., P.S. and C.C. contributed to data collection and/or performed surgical procedures. M.C.L., P.S. and C.C. analysed and interpreted the data. M.-C.L.P. performed expert statistical review. All authors contributed to the writing of the manuscript. P.S. and C.C. revised critically the final version of the manuscript. All authors approved the final submitted version of the manuscript.

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## Conflict of interest

None declared.

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