Human Reproduction, Vol.30, No.2 pp. 299–307, 2015
Advanced Access publication on November 28, 2014 doi:10.1093/humrep/deu308

human reproduction

ORIGINAL ARTICLE ***Gynaecology***

Endometriotic ovarian cysts do not negatively affect the rate of spontaneous ovulation

U. Leone Roberti Maggiore*, C. Scala, P.L. Venturini, V. Remorgida, and S. Ferrero

Obstetrics and Gynaecology Unit, IRCCS San Martino Hospital and National Institute for Cancer Research, University of Genoa, 16132 Genoa, Italy

*Correspondence address. Obstetrics and Gynaecology Unit, IRCCS San Martino Hospital and National Institute for Cancer Research, University of Genoa, 16132 Genoa, Italy. Tel: +39-01139-010511525; Fax: +39-01139-010511525; E-mail: ulrm@me.com

Submitted on January 25, 2014; resubmitted on October 5, 2014; accepted on October 28, 2014

STUDY QUESTION: Do endometriotic ovarian cysts influence the rate of spontaneous ovulation?

SUMMARY ANSWER: Endometriotic cysts, no matter what their volume, do not influence the rate of spontaneous ovulation in the affected ovary.

WHAT IS KNOWN ALREADY: Endometriotic ovarian cysts may negatively affect spontaneous ovulation in the affected ovary.

STUDY DESIGN, SIZE, DURATION: This was a prospective observational study performed between September 2009 and June 2013.

PARTICIPANTS/MATERIALS, SETTING, METHODS: This study included women of reproductive age with regular menstrual cycles and unilateral ovarian endometriomas (diameter ≥20 mm) desiring to conceive. Exclusion criteria were: hormonal therapies in the 3 months prior to study entry and previous adnexal surgery. Patients underwent serial transvaginal ultrasound to assess the side of ovulation (for up to six cycles).

MAIN RESULTS AND THE ROLE OF CHANCE: Ovulation was monitored in 1199 cycles in 244 women (age, mean ± SD, 34.3 ± 4.9 years). 55.3% of the patients had left endometriomas and 44.7% had right endometriomas ($P = 0.024$). The mean (± SD) diameter of the endometriomas was 5.3 cm (± 1.7 cm). Ultrasonographically documented ovulation occurred in 596 cycles in the healthy ovary (49.7%; 95% CI, 46.8–52.6%) and in 603 cycles in the affected ovary (50.3%; 95% CI, 47.1–53.2%; $P = 0.919$). This observation was confirmed in patients with diameter of the cyst ≥4 cm ($n = 166$) and in those with diameter of the cyst ≥6 cm ($n = 45$). One hundred and five patients spontaneously conceived (43.0%; 95% CI, 36.7–49.5%).

LIMITATIONS, REASON FOR CAUTION: The high pregnancy rate reported in this study was observed in a selected population of women with endometriomas and cannot be extrapolated to all patients with endometriosis.

WIDER IMPLICATIONS OF THE FINDINGS: Since ovarian endometriomas do not impair spontaneous ovulation, the impact on fertility of surgical excision of ovarian endometriomas should be further investigated.

STUDY FUNDING/COMPETING INTEREST(S): None.

TRIAL REGISTRATION NUMBER: None.

Key words: endometriosis / female infertility / menstrual cycle / ovulation / ultrasound

Introduction

At least 4% of reproductive age women are affected by endometriosis (Ferrero *et al.*, 2010). Ovarian endometriomas are a typical manifestation of the disease and their prevalence is between 17 and 44% of patients with endometriosis (Jenkins *et al.*, 1986; Redwine, 1999; Busacca and Vignali, 2003). Ovarian endometriotic cysts are more frequently located on the left ovary (~60%); this is justified by the menstrual reflux theory and the anatomical differences between the left and right hemipelvis (Vercellini *et al.*, 2002; Ferrero *et al.*, 2005). Ovarian endometriomas may be treated by hormonal therapies which cause a decrease in their volume (Donnez *et al.*, 1989; Rana *et al.*, 1996; Lall *et al.*, 2011; Muneyyirci-Delale *et al.*, 2012; Del Forno *et al.*, 2013; Ferrero *et al.*, 2013); however, when these therapies are discontinued, ovarian

endometriotic cysts frequently grow. Alternatively, endometriomas may be excised at laparoscopy. However, the recurrence rate of endometriomas after surgery is between 11.7 and 30.4% at 2–5 years follow-up (Busacca *et al.*, 1999; Ghezzi *et al.*, 2001; Jones and Sutton, 2002; Koga *et al.*, 2006). Furthermore, surgical treatment of ovarian endometriotic cysts may decrease the ovarian reserve (Ferrero *et al.*, 2012; Raffi *et al.*, 2012; Somigliana *et al.*, 2012, Uncu *et al.*, 2013). During surgery, healthy ovarian tissue may be inadvertently removed (Muzii *et al.*, 2005, 2007) particularly when the procedure is performed by surgeons with limited experience (Muzii *et al.*, 2011). Furthermore, the impairment of ovarian reserve may also be related to the presence of the ovarian endometriotic cysts *per se*. A histological investigation of the functional morphologic features of the ovarian cortex surrounding benign cysts demonstrated that endometriomas are associated with reduced follicular number and activity compared with teratomas or other benign cystadenomas (Maneschi *et al.*, 1993). Recently, Uncu *et al.* (2013) observed that women with endometriomas have lower anti-Mullerian hormone (AMH) levels and antral follicle count compared with women who do not have ovarian cysts, suggesting that the presence of endometrioma *per se* is associated with a reduction in ovarian reserve.

A study investigating the rate of spontaneous ovulation in patients with unilateral endometrioma suggested that endometriotic cysts have a detrimental impact on ovarian physiology; the ratio of the rate of ovulation between healthy and affected ovaries was about 2:1 (Benaglia *et al.*, 2009). To further investigate this topic, a wider prospective study was designed to monitor for up to six ovulatory cycles the rate of spontaneous ovulation in patients with unilateral endometriomas.

Material and Methods

Study design

This prospective observational study was performed between September 2009 and June 2013. The study protocol was approved by the local Research Review Committee. Women participated in the study after an informed written consent was obtained. The primary end-point of the study was to evaluate the rate of ultrasonographically documented ovulation between the healthy and affected ovary in women with unilateral endometriomas. The secondary end-point was to evaluate the pregnancy rate in this population.

Study population

The study included women of reproductive age, desiring to conceive, with ultrasonographic diagnosis of unilateral ovarian endometriotic cysts (diameter $\geq$20 mm). Additional criteria for inclusion in the study were: regular menstrual cycle (24–35 days) and male partners with normal semen analysis (accordingly to the World Health Organization criteria). The exclusion criteria for the study were: previous adnexal surgery; use of hormonal therapies in the 3 months prior to inclusion in the study; pregnancy or breastfeeding in the 6 months prior to inclusion in the study; ultrasonographic diagnosis of hydrosalpinx or history of pelvic inflammatory disease; history of infertility (with or without previous use of infertility therapies); polycystic ovary syndrome (PCOS); thyroid disorders; psychiatric disturbances and history of drug or alcohol abuse.

Study protocol

Ultrasonographic evaluation of the ovarian endometriotic cyst

The diagnosis of ovarian endometriotic cysts was based on transvaginal ultrasonography, which was performed by two experienced ultrasonographers (U.L.R.M. and S.F.) by using a Voluson E6 ultrasound machine (General Electric Medical Systems, Milwaukee, WI, USA). Ovarian endometriotic cysts were diagnosed when a round-shaped cystic mass with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes, and without papillary projections was observed (Mais *et al.*, 1993).

After the diagnosis of unilateral ovarian endometriotic cysts, patients were invited to participate to the study. Patients accepting to participate to the study underwent, after 2 months, a second transvaginal ultrasonography. If the diagnosis of unilateral ovarian endometriotic cysts was confirmed, the volume of the cyst was measured (baseline assessment). The volume of the ovarian endometriotic cysts was estimated by using the virtual organ computer-aided analysis (VOCAL, GE Healthcare, Milwaukee, WI, USA) as previously described (Ferrero *et al.*, 2013). Briefly, the VOCAL technique was used to obtain a sequence of 20 sections of each ovarian cyst around a fixed axis, each after 9° rotation from the previous section, which represents the best compromise between reliability, validity and time to define the volume (Raine-Fenning *et al.*, 2003). The contour of each cyst was drawn manually by using the roller ball cursor of the 3D ultrasound machine to obtain a 3D volume measurement. The measurements were performed off-line after scanning. In addition, the largest diameter of the endometrioma was recorded. The volume of the endometriomas and the largest diameter of the cyst were assessed at baseline and then at the sixth ovulatory cycle, unless the patient withdrew from the study, used hormonal therapy, underwent surgery or had conceived.

Assessment of ovulation and endometrial thickness

Patients underwent daily serial transvaginal ultrasounds to determine the side of ovulation starting on Day 6–8 of the menstrual cycle for up to six ovulatory cycles. The ultrasonographically documented ovulation was defined as the presence of a growing leading follicle and the subsequent development of corpus luteum. The day of ultrasonographically documented ovulation was considered Day 0 and the preceding Days −1, −2, −3, −4.

Furthermore, the endometrial thickness was evaluated by aligning the uterus along the central longitudinal axis; it was measured from the echogenic interface between the endometrium and myometrium to the opposite interface at the point of maximum thickness.

Assessment of non-ovarian endometriosis

All patients underwent a detailed ultrasonographic assessment when the second transvaginal ultrasonography was performed to confirm the diagnosis of ovarian endometrioma. In particular, the presence of endometriotic nodules in the following locations was systematically assessed: rectovaginal septum, vagina, rectum-sigmod, uterosacral ligaments, bladder. Endometriotic nodules were typically visualized as hypoechoic or isoechogenic solid masses with irregular outer margins (Bazot and Darai, 2005). The largest diameter of any deep nodule was recorded.

Assessment of ovarian reserve and cancer antigen-125 (CA-125)

Venous blood samples were drawn on Day 3 of the menstrual cycle at baseline assessment. Ovarian reserve was estimated by measuring the levels of AMH and FSH. AMH was assayed with AMH Gen II ELISA (Beckman Coulter, Inc., Brea, CA, USA). FSH and CA-125 levels were analysed with the Immulite 2000 XPi immunoassay system (Siemens Healthcare Diagnostics, Milan, Italy).

Assessment of symptoms

The intensity of pain symptoms (dysmenorrhea, non-menstrual pelvic pain and deep dyspareunia) was measured using a 10 cm visual analogue scale (VAS), the left extreme of the scale indicating the absence of pain, and the right indicating the pain as bad as it could be. The intensity of pain symptoms was evaluated at baseline and at the sixth ovulatory cycle immediately before

the first ultrasonography used to assess the side of ovulation (Day 6–8 of the menstrual cycle). At each assessment patients were requested to judge the severity of the pain perceived in the last month.

Statistical analysis

Both in the total study population and in the subanalyses (side of the endometrioma, number of endometriomas and size of the endometriomas), the rate of ultrasonographically documented ovulation in the healthy and affected ovary was presented as percentage and 95% confidence interval (CI) of the percentage. The normal distribution of continuous variable data was evaluated with the Kolmogorov–Smirnov test. Categorical variables were compared by using the chi-square test and the Fisher exact test according to sample size. Continuous variables were compared by using *t*-test or Mann–Whitney test according to data distribution. A Bonferroni correction was applied to the significance levels obtained to determine whether the observed significant differences in endometrial thickness and in main diameter of the leading follicle between women ovulating in the healthy ovary or in the affected ovary may have occurred due to multiple analyses. The correlation between FSH, AMH, CA-125 and volume and main diameter of the endometriomas was assessed by using the Spearman correlation coefficient. The Kruskal–Wallis one way analysis of variance on ranks was used to compare FSH, AMH and CA-125 levels in patients with different number of endometriomas. Data were analysed using the SPSS software version 20.0 (SPSS Science, Chicago, IL, USA).

Results

Three hundred and forty-three patients were invited to participate in the study, 278 (81.0%) agreed and 244 (71.6%) were finally included. Women included in the study had a mean ± SD age of 34.3 ± 4.9 years and a mean ± SD BMI of 22.5 ± 1.9 kg/m^2. Twenty-seven patients (11.1%) had previous live births and the median (range) parity was 0 (0–1). Sixty-one patients (25.0%) had no evidence of deep endometriosis. One hundred thirty-six patients (55.7%) had endometriotic nodules on the uterosacral ligament on the side of the endometrioma, mean ± SD diameter 12.4 ± 4.9 mm (range, 5–26 mm); 58 patients (23.8%) had endometriotic nodules on the uterosacral ligament contralateral to the endometrioma, mean ± SD diameter 12.1 ± 4.7 mm (range, 5–22 mm); 67 patients (27.5%) had rectovaginal endometriotic nodules, mean ± SD diameter 14.2 ± 5.1 mm (range, 8–28 mm); 13 patients (5.3%) had vaginal nodules, mean ± SD diameter 11.4 ± 2.6 mm (range, 7–16 mm); 4 patients (1.6%) had rectum-sigmoid endometriotic nodules, mean ± SD diameter 22.3 (± 3.8) mm (range, 18–27 mm); and 2 patients (0.8%) had bladder nodules, respectively with larger diameter of 23 and 28 mm.

At baseline, the mean ± SD levels of FSH, AMH and CA-125 were 6.89 ± 2.04 mIU/ml, 2.79 ± 1.37 ng/ml and 39.5 ± 25.6 IU/ml, respectively. Figure 1 summarizes the flow of the patients during the study. Supplementary Table SI shows that there was no correlation between FSH, AMH, CA-125 levels and size, laterality and number of the ovarian endometriotic cysts at baseline.

Characteristics of ovarian endometriotic cysts

Endometriomas were located more frequently on the left ovary ($n = 135$; 55.3%) than on the right ovary ($n = 109$; 44.7%; $P = 0.024$). One hundred and ninety-eight (81.1%) patients had single endometrioma, 37 (15.2%) had two endometriomas and 9 (3.7%) had three endometriomas. The mean ± SD largest diameter of endometriomas at baseline was 5.3 ± 1.7 cm. At baseline, 166 patients (55.5%) had endometriomas with

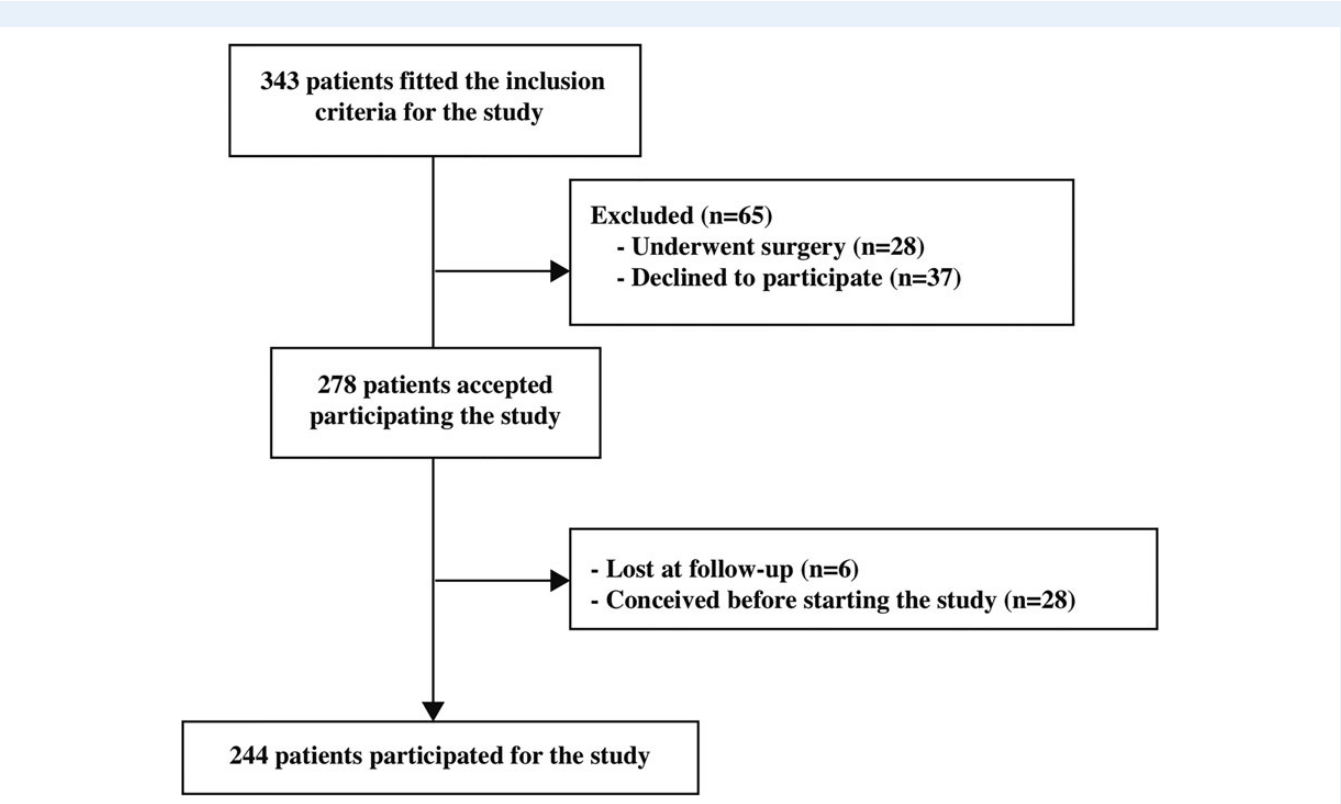

Figure 1 Flow of the patients during the study.

largest diameter ≥40 mm and 45 (15.1%) had endometriomas with a largest diameter ≥60 mm. The mean ± SD volume of the endometriomas at baseline was 54.9 ± 52.5 cm^3.

Characteristics of spontaneous ovulation during the study

Table I describes the distribution of ultrasonographically documented ovulation between the healthy and affected ovary during the study. A total of 1311 cycles were evaluated. In 112 cycles (8.5%; 95% CI, 7.1–10.2%) it was not possible to clearly identify the ovulation. No significant difference in the rate of ultrasonographically documented ovulation was observed between the healthy (50.3%; 95% CI 47.1–53.2%) and the affected ovary (49.7%; 95% CI 46.8–52.6%; $P = 0.842$; Fig. 2). As summarized in Table II, the rate of ultrasonographically documented ovulation between the affected and the healthy ovary was not affected by the laterality of endometriomas, their number and size. Furthermore, the

Table I Distribution of ultrasonographically documented ovulation during the study between the healthy and the affected ovary.

	Healthy ovary (*n*, %; 95% CI)	Affected ovary (*n*, %; 95% CI)	*P*
All diameters of the cysts:			
Cycle 1 ($n = 244$)*	118 (48,4; 41.9–54.8)	126 (51.6; 45.2–58.1)	0.786
Cycle 2 ($n = 238$)*	121 (50.8; 44.3–57.4)	117 (49.2; 42.6–55.7)	0.927
Cycle 3 ($n = 224$)*	109 (48.7; 41.9–55.4)	115 (51.3; 44.6–58.1)	0.850
Cycle 4 ($n = 210$)*	103 (49.0; 42.1–56.0)	107 (51.0; 44.0–57.9)	0.922
Cycle 5 ($n = 156$)*	75 (48.1; 40.0–56.2)	81 (51.9; 43.8–60.0)	0.821
Cycle 6 ($n = 127$)*	63 (49.6; 40.6–58.6)	64 (50.4; 41.4–59.4)	0.950
Total	596 (49.7; 46.8–52.6)	603 (50.3; 47.1–53.2)	0.919

*Number of patients.

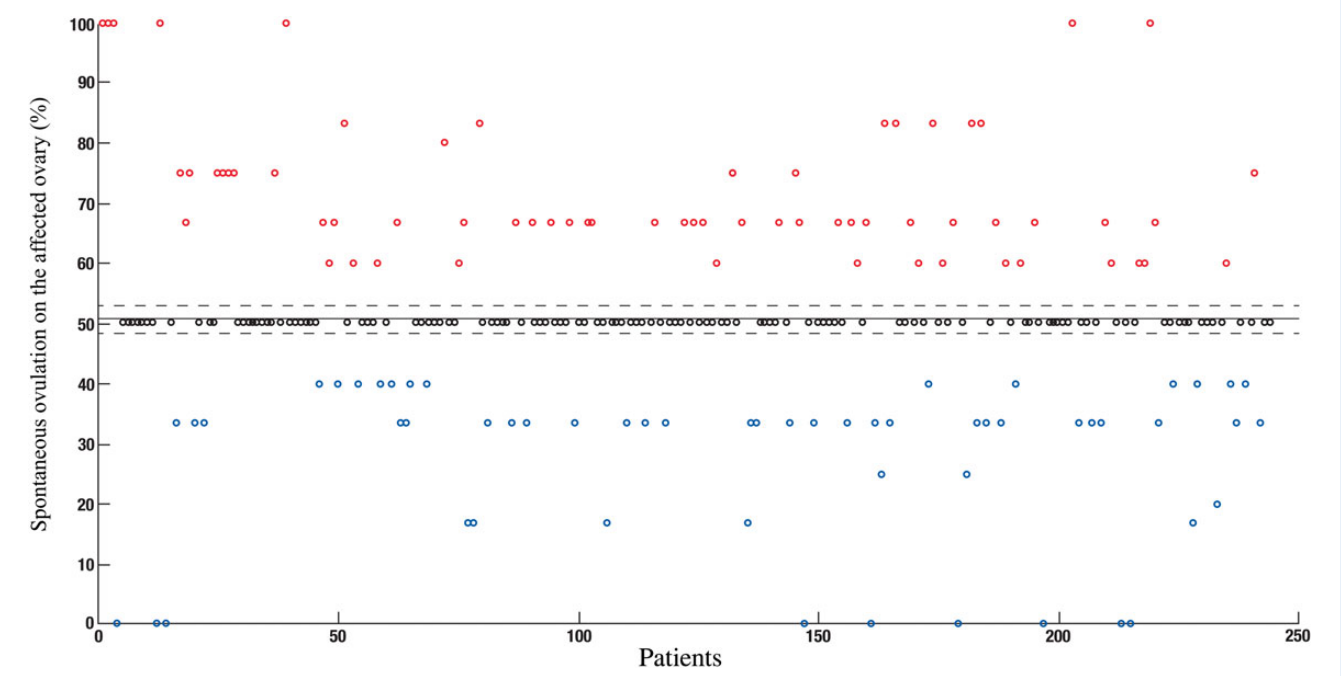

Figure 2 Percentage of cycles when each patient demonstrated ultrasonographically documented ovulation from the affected ovary. The scatter plot represents the percentage of ultrasonographically documented ovulation for each patient on the affected ovary; each patient is represented by a circle. The continuous black line indicates the mean percentage rate of ultrasonographically documented ovulation on the affected ovary in the entire study population. The interrupted black lines indicate the 5 and 95% limits of the confidence interval of the mean percentage. Blue circles are used to indicate the patients with a percentage rate of ultrasonographically documented ovulation on the affected ovary that is below the 5% limit of the confidence interval of the mean percentage. Red circles are used to indicate the patients with a percentage rate of ultrasonographically documented ovulation on the affected ovary that is over the 95% limit of the confidence interval of the mean percentage. Black circles are used to indicate the patients with a percentage rate of ultrasonographically documented ovulation on the affected ovary that is between the 5 and 95% limits of the confidence interval of the mean percentage.

Table II Main characteristics of endometriomas.

Population	Number of cases (*n*, %)	Ultrasonographically documented ovulation in the affected ovary during 6 ovulatory cycles		*P**
		Number	% (95% CI)	
Side of the endometrioma:				
Right	109 (44.9)	272	49.4 (45.1–53.6)	0.880
Left	135 (55.6)	331	50.6 (46.4–54.9)	0.825
Number of cysts:				
1	198 (81.1)	486	50.5 (47.3–53.7)	0.873
2	37 (15.2)	97	49.5 (42.3–56.7)	0.920
3	9 (3.7)	20	50.0 (33.8–66.2)	1.0
Main diameter of the endometrioma:				
≥40 mm	166 (55.5)	454	53.0 (49.6–56.4)	0.236
≥60 mm	45 (15.1)	134	51.9 (45.7–58.2)	0.725
Deep endometriosis:				
No	61 (25.0)	141	50.0 (44.2–55.8)	1
Yes	183 (75.0)	462	50.4 (47.2–53.6)	0.926

*The *P*-value refers to the comparison between the healthy and the affected ovary.

rate of ultrasonographically documented ovulation between the affected and the healthy ovary was not affected by the diagnosis of deep endometriosis at transvaginal ultrasonography.

Characteristics of endometrial thickness and of the leading follicle during the study

Table III summarizes the measurements of endometrial thickness which were recorded during Day 0, −1, −2, −3 and −4 of each cycle. Table IV shows the measurements of the main diameter of the leading follicle which were evaluated during Day 0, −1, −2, −3 and −4 of each cycle.

Patients progression through the study and pregnancy rate

A total of 127 patients (52.3%; 95% CI 45,8–58.7%) completed the 6 cycles of the study protocol. The causes of withdrawal are listed in Table V. Following the six spontaneous ovulations monitored during the study, 105 patients conceived (43.2%; 95% CI, 36.9–49.7%). No statistical difference was reported in the side of ovulation (healthy or affected ovary) at the time of conceiving. The pregnancy outcome is reported in Table V.

Characteristics of ovarian endometriotic cysts and of pain symptoms at the end of the study protocol

A mean (95% CI) increase of 8.1% (6.6–9.6%) in the volume of the ovarian endometriotic cysts was observed between baseline (mean ± SEM, 54.9 ± 4.7 cm^3) and sixth ovarian cycle (59.1 ± 4.9 cm^3; $P < 0.001$). Figure 3 shows the per cent changes in the volume of the endometriomas at sixth ovarian cycle in the study population. There was a mean (95% CI) increase of 3.9% (3.1–4.7%) in the largest diameter of the ovarian endometriotic cysts between baseline (mean ± SD, 5.3 ± 1.7 cm) and sixth ovarian cycle (5.6 ± 1.8 cm; $P < 0.001$). The number of patients reporting pain symptoms and the intensity of these symptoms were similar between baseline and sixth ovarian cycle (Table VI).

Discussion

In the last decade great attention has been given to the impact of endometriomas on ovarian physiology. Benaglia *et al.* (2009) observed that in a population of women with unilateral endometriomas assessed for one ovarian cycle, spontaneous ovulation occurred more frequently in the healthy ovary than in the affected one. In that study, the number of cysts and their side seemed to influence the rate of spontaneous ovulation between the two ovaries, while the size did not. In contrast, the current study with a larger sample size shows that, in patients with unilateral ovarian endometriotic cysts assessed for a period of six ovarian cycles, the rate of ultrasonographically documented ovulation was similar between the healthy and the affected ovary. Furthermore, this study showed that the rate of ultrasonographically documented ovulation between the two ovaries was not affected by the laterality of endometriomas, their number and size, and by the ultrasonographic diagnosis of deep endometriosis.

The role of endometriomas on ovarian physiology is quite controversial. Initially, it was suggested that the presence of ovarian endometriotic cysts was associated with decreased antral follicle count and with a reduction in the number of oocytes retrieved for *in vitro* fertilization (IVF) (Yanushpolsky *et al.*, 1998; Suzuki *et al.*, 2005; Kumbak *et al.*, 2008; Almog *et al.*, 2010). However, these findings were contradicted by more recent investigations showing that the number of antral follicles and oocytes retrieved were not affected by the presence of endometriomas (Tocci *et al.*, 2010; Almog *et al.*, 2011; Kiran *et al.*, 2012). Similar

Table III Endometrial thickness (mm; mean ± SD).

	Patients ovulating in the healthy ovary	Patients ovulating in the affected ovary	P
Cycle 1			
Day 0	11.5 ± 2.8	11.8 ± 3.0	0.274
Day −1	10.4 ± 2.7	10.6 ± 2.7	0.508
Day −2	9.4 ± 2.5	9.6 ± 2.4	0.501
Day −3	8.5 ± 2.1	8.7 ± 2.2	0.431
Day −4	7.5 ± 1.9	7.8 ± 2.1	0.274
Cycle 2			
Day 0	11.8 ± 3.1	11.4 ± 2.9	0.485
Day −1	10.5 ± 2.9	10.4 ± 2.7	0.986
Day −2	9.6 ± 2.7	9.5 ± 2.6	0.941
Day −3	8.7 ± 2.5	8.6 ± 2.3	0.983
Day −4	7.9 ± 2.4	7.8 ± 2.2	0.880
Cycle 3			
Day 0	11.8 ± 2.8	11.6 ± 3.1	0.468
Day −1	10.6 ± 2.7	10.4 ± 2.9	0.330
Day −2	9.6 ± 2.4	9.4 ± 2.7	0.257
Day −3	8.6 ± 2.1	8.6 ± 2.4	0.534
Day −4	7.7 ± 2.0	7.7 ± 2.4	0.773
Cycle 4			
Day 0	11.3 ± 3.0	11.7 ± 3.2	0.270
Day −1	10.3 ± 2.8	10.4 ± 2.9	0.702
Day −2	9.2 ± 2.6	9.4 ± 2.7	0.687
Day −3	8.2 ± 2.2	8.6 ± 2.5	0.189
Day −4	7.2 ± 2.1	7.8 ± 2.4	0.043*
Cycle 5			
Day 0	11.7 ± 2.8	11.5 ± 2.9	0.607
Day −1	10.6 ± 2.6	10.2 ± 2.7	0.161
Day −2	9.5 ± 2.4	9.2 ± 2.5	0.200
Day −3	8.5 ± 2.0	8.4 ± 2.2	0.624
Day −4	7.4 ± 1.9	7.6 ± 2.1	0.713
Cycle 6			
Day 0	11.8 ± 2.7	11.9 ± 3.0	0.960
Day −1	10.8 ± 2.5	10.6 ± 2.8	0.489
Day −2	9.7 ± 2.3	9.6 ± 2.5	0.520
Day −3	8.6 ± 2.0	8.7 ± 2.3	0.973
Day −4	7.5 ± 2.0	7.8 ± 2.1	0.433

*Not significant after Bonferroni correction.

Table IV Main diameter of the leading follicle (mm; mean ± SD).

	Patients ovulating in the healthy ovary	Patients ovulating in the affected ovary	P
Cycle 1			
Day 0	21.2 ± 1.7	21.5 ± 1.9	0.967
Day −1	20.1 ± 1.6	20.3 ± 1.8	0.675
Day −2	18.9 ± 1.5	19.1 ± 1.7	0.920
Day −3	17.7 ± 1.4	17.8 ± 1.7	0.815
Day −4	16.2 ± 1.5	16.4 ± 1.6	0.530
Cycle 2			
Day 0	21.6 ± 1.7	21.4 ± 2.0	0.307
Day −1	20.4 ± 1.6	20.2 ± 1.9	0.175
Day −2	19.3 ± 1.5	19.1 ± 1.8	0.187
Day −3	18.1 ± 1.6	17.9 ± 1.8	0.287
Day −4	16.7 ± 1.6	16.3 ± 1.7	0.095
Cycle 3			
Day 0	21.2 ± 2.1	21.6 ± 2.1	0.299
Day −1	20.2 ± 2.1	20.4 ± 1.9	0.487
Day −2	19.0 ± 1.9	19.3 ± 2.0	0.309
Day −3	17.7 ± 1.9	18.0 ± 1.9	0.267
Day −4	16.1 ± 2.0	16.3 ± 1.7	0.370
Cycle 4			
Day 0	21.5 ± 2.4	21.5 ± 1.6	0.479
Day −1	20.3 ± 2.3	20.3 ± 1.4	0.665
Day −2	19.2 ± 2.2	19.0 ± 1.5	0.183
Day −3	18.0 ± 2.3	17.7 ± 1.5	0.127
Day −4	16.4 ± 2.1	16.1 ± 1.4	0.048*
Cycle 5			
Day 0	21.0 ± 2.5	21.3 ± 2.5	0.211
Day −1	19.8 ± 2.3	20.1 ± 2.4	0.313
Day −2	18.6 ± 2.4	19.1 ± 2.4	0.089
Day −3	17.5 ± 2.3	17.9 ± 2.3	0.067
Day −4	15.8 ± 2.2	16.4 ± 2.3	0.053
Cycle 6			
Day 0	21.3 ± 2.1	21.7 ± 1.6	0.123
Day −1	20.1 ± 1.9	20.5 ± 1.5	0.169
Day −2	19.0 ± 2.0	19.3 ± 1.4	0.210
Day −3	17.8 ± 2.0	18.0 ± 1.4	0.297
Day −4	16.1 ± 1.8	16.4 ± 1.3	0.261

*Not significant after Bonferroni correction.

findings were reported for the quality of embryos obtained in patients with endometriomas who underwent IVF. Some studies suggested that the presence of endometriomas may affect embryo quality (Yanushpolsky *et al.*, 1998; Kumbak *et al.*, 2008), but these results were not confirmed by other investigations demonstrating that endometriotic ovarian cysts did not negatively influence embryo quality (Tinkanen and Kujansuu, 2000; Suzuki *et al.*, 2005; Tocci *et al.*, 2010; Reinblatt *et al.*, 2011). On the basis of this contradictory literature, it is difficult to specify the correct management of ovarian endometriotic cysts in women with fertility expectation.

A finding of the current study is that 43.0% of the patients conceived during the 6-month study period. Although several studies reported the reproductive performance after surgical excision of endometriomas (Shimizu *et al.*, 2010; Raffi and Amer, 2013), surprisingly no data are available on the spontaneous pregnancy rate of patients with endometriosis without a history of infertility. The high pregnancy rate observed in the current study may be explained by the fact that the patients had unilateral endometriomas, no history of infertility, no risk factors for tubal disease

Table V Characteristics of withdrawal and pregnancy outcome.

Withdrawal time (median, 25th–75th percentiles, number of cycle)	5 (4–5.3)
Causes of withdrawal (*n*, %)	
Lost at follow-up	14 (12.0%)
Hormonal therapies	8 (6.8%)
Surgery	5 (4.3%)
Pregnancies	90 (76.9%)
Total	117 (100%)
Pregnancies	
Number of patients conceiving during the study protocol (*n*, %)	105 (43.0%)
Patients conceiving during the study protocol (*n*, %)*	
without concomitant deep endometriosis	29 (47.5%; 35.0–60.0%)
with concomitant deep endometriosis	76 (41.5%; 34.4–48.6%)
Last cycle evaluated before conceiving (median, median, 25th–75th percentiles)	4 (3–5)
Side of ovulation when conceiving (*n*, %; 95% CI)**	
Healthy ovary	56 (53.3%; 43.3–63.1%)
Affected ovary	49 (46.7%; 36.9–56.7%)
Pregnancy outcome (*n*, %)	
Miscarriages	11 (10.5%)
Second trimester voluntary termination of pregnancy	2 (1.9%)
Pre-term pregnancies	4 (3.8%)
Term pregnancies	67 (63.8%)
Ongoing pregnancies	21 (20.0%)
Delivery outcome (*n*, %)	
Spontaneous delivery	76 (72.4%)
Operative delivery	6 (5.7%)
Caesarean section	23 (21.9%)

*$P = 0.502$; **$P = 0.408$.

(such as history of pelvic inflammatory disease) and their male partners had normal semen analysis. In addition, it is relevant that there was no significant difference in the side of ovulation (healthy or affected ovary) when the patients conceived. These findings should be considered when choosing the best treatment of endometriomas in women desiring to conceive. The high spontaneous pregnancy rate observed in the current study suggests that surgery should not be routinely offered to women with endometriomas without history of infertility with the aim to improve fertility. These patients should try to spontaneously conceive, particularly if they have no risk factor for tubal disease and if their male partners have normal semen analysis. Recently, the ESHRE guideline on the 'Management of women with endometriosis' suggests that in case of single ovarian endometriotic cysts with diameter between 3 and 6 cm, surgery may be not useful before ART (ESHRE, 2013). The findings of the current study suggest that surgery may not be required in patients without a history of infertility desiring to conceive. The availability of histological confirmation of endometrioma diagnosis, the improvement of endometriosis-related pain, lysis of adhesions and tubal patency evaluation may be points in favour of laparoscopic treatment of endometriomas. However, patients without a history of infertility undergoing surgery because of endometriomas should be informed on the risk of ovarian function damage (Raffi *et al.*, 2012; Somigliana *et al.*, 2012) and ovary loss (Busacca *et al.*, 2006) and of the lack of improved clinical pregnancy rate in case of ART (Hart *et al.*, 2008; Benschop *et al.*, 2010; ESHRE, 2013).

Another finding of this study was that, during the 6-month study period, there was an increase in the volume of endometriomas. This observation suggests that endometriomas size may progress and surgery may be considered in patients who do not conceive after a reasonable period of time (between 6 and 12 months). While it is well known that hormonal treatments decrease the size of endometriomas (Donnez *et al.*, 1989; Ferrero *et al.*, 2013), no data are available on the changes in the size of endometriomas during long-term follow-up of patients who do not use hormonal therapies and did not undergo previous surgery.

Unfortunately, in the current study we did not investigate the size of the endometriomas during pregnancy. A retrospective study analysed the changes in the size of endometrioma during pregnancy showing that among 25 ovarian endometriotic lesions observed in 24 women (one patient had two lesions), the size of the cyst decreased in 13 cases (52%), did not modify in 7 cases (28%), and increased in 5 cases (20%) (Ueda *et al.*, 2010). More recently, a prospective cohort study including 24 women carrying endometriomas at the time of *in vitro* fertilization who got pregnant, demonstrated that a consistent proportion of small cysts (mean diameter of all cysts <20 mm) becomes undetectable after delivery. In fact, 12–18 months after oocyte retrieval, the number of cysts per patient was unchanged in 8 cases (33%), increased in 2 cases (8%) and decreased in 14 cases (59%). In 11 of these latter cases (46% of the total), no endometrioma could be detected (Benaglia *et al.*, 2013).

Another limitation of this study is the lack of evaluation of the presence of adhesions and of ovarian mobility. Adhesions are a typical manifestation of endometriosis and in patients affected by endometriomas they may develop among the cyst, pelvic wall, bowel and uterus. The most accepted classification of the disease, the revised American Society of Reproductive Medicine Classification, rASRM, underlines the relevant role of adhesions in endometriosis; in fact, their presence significantly influences the total score. It should be considered that rASRM is part of the Endometriosis Fertility Index, a classification, which has been demonstrated to estimate effectively the chances of pregnancy after surgery (Adamson and Pasta, 2010). Previous studies proved that transvaginal ultrasonography has good specificity and sensitivity (90 and 89%, respectively) in the assessment of adhesions and of ovarian mobility (Guerriero *et al.*, 1997; Okaro *et al.*, 2006; Holland *et al.*, 2010, 2013). Therefore, due to the fact that the presence of ovarian adhesions was not assessed, it was not possible to estimate the impact of ovarian adhesions on the rate of spontaneous pregnancies.

In conclusion, the current study shows that endometriotic cysts, irrespective of their volume, do not influence the rate of spontaneous ovulation in the affected ovary. Furthermore, this study demonstrates for the first time that patients with unilateral endometriomas have good spontaneous pregnancy rate if the couple has no other risk factor for infertility. Future investigation should assess the spontaneous pregnancy rate in patients with other endometriotic lesions (such as rectovaginal nodules and bilateral endometriomas).

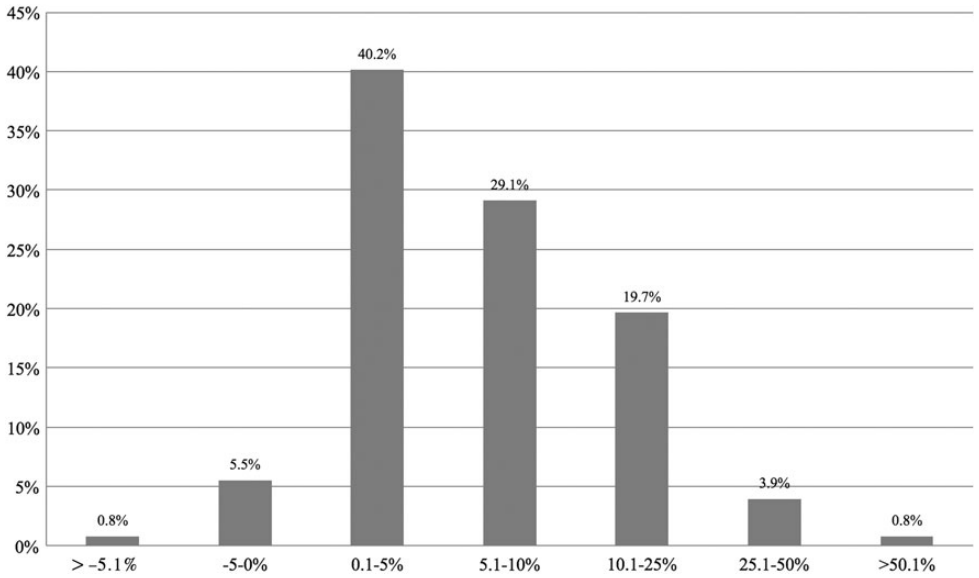

Figure 3 Percentage of patients that exhibited changes of the size of the endometriomas by the sixth ovarian cycle, according to the percentage variation of the volume.

Table VI Characteristics of pain symptoms.

	Baseline (n = 244)	6th ovarian cycle (n = 127)	P
Dysmenorrhoea	161 (66.0) 4.4 ± 1.0	83 (65.4) 4.7 ± 1.4	0.995 0.125
Dyspareunia	79 (32.4) 3.7 ± 1.4	39 (30.7) 4.1 ± 1.8	0.834 0.191
Chronic pelvic pain	96 (39.3) 4.0 ± 1.5	51 (40.2) 4.2 ± 1.8	0.968 0.702

Data are n(%), mean ± SD position on visual analogue scale (cm).

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' roles

U.L.R.M.: recruited the patients enrolled in the study and performed the follow-up; performed the statistical analyses; prepared the draft of the manuscript. C.S.: recruited the patients enrolled in the study and performed the follow-up. P.L.V.: supervised the whole study procedure including the design of the study and interpretation of results; revised the manuscript. V.R.: supervised the whole study procedure including the design of the study and interpretation of results; revised the manuscript. S.F.: had the original idea of the study; performed the follow-up; performed the statistical analyses; revised the manuscript.

Funding

No funding was received for this study.

Conflict of interest

None declared.

References

Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. *Fertil Steril* 2010;**94**:1609–1615.

Almog B, Shehata F, Sheizaf B, Tulandi T. Effect of different types of ovarian cyst on antral follicle count. *Fertil Steril* 2010;**94**:2338–2339.

Almog B, Shehata F, Sheizaf B, Tan SL, Tulandi T. Effects of ovarian endometrioma on the number of oocytes retrieved for *in vitro* fertilization. *Fertil Steril* 2011;**95**:525–527.

Bazot M, Darai E. Sonography and MR imaging for the assessment of deep pelvic endometriosis. *J Minim Invasive Gynecol* 2005;**12**:178–185.

Benaglia L, Somigliana E, Vercellini P, Abbiati A, Ragni G, Fedele L. Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation. *Hum Reprod* 2009;**24**:2183–2186.

Benaglia L, Somigliana E, Calzolari L, Busnelli A, Cardellicchio L, Ragni G, Fedele L. The vanishing endometrioma: the intriguing impact of pregnancy on small endometriotic ovarian cysts. *Gynecol Endocrinol* 2013;**29**:863–866.

Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010;**11**:CD008571.

Busacca M, Vignali M. Ovarian endometriosis: from pathogenesis to surgical treatment. *Curr Opin Obstet Gynecol* 2003;**15**:321–326.

Busacca M, Marana R, Caruana P, Candiani M, Muzii L, Calia C, Bianchi S. Recurrence of ovarian endometrioma after laparoscopic excision. *Am J Obstet Gynecol* 1999;**180**:519–523.

Busacca M, Riparini J, Somigliana E, Oggioni G, Izzo S, Vignali M, Candiani M. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. *Am J Obstet Gynecol* 2006;**195**:421–425.

Del Forno S, Solfrini S, Ferrini G, Zannoni L, Bertoldo V, Monti G, Leonardi D, Morselli Labate AM, Paccapelo A, Seracchioli R. Do low-dose oral contraceptives have an effect on ovarian endometrioma diameter and endometriosis symptoms? *J Endometr* 2013;**5**:151–158.

Donnez J, Nisolle-Pochet M, Clerckx-Braun F, Sandow J, Casanas-Roux F. Administration of nasal Buserelin as compared with subcutaneous Buserelin implant for endometriosis. *Fertil Steril* 1989;**52**:27–30.

European Society of Human Reproduction and Embryology. Management of women with endometriosis. Available at: http://www.eshre.eu/binarydata.aspx?type=doc&sessionId=dhxqnrv5jhqpiw45ttwpuxup/ESHRE_ENDOMETRIOSIS_GUIDELINE_Draft_version_for_review.pdf. Accessed April 23, 2013.

Ferrero S, Ragni N, Fulcheri E. Lateral distribution of benign ovarian cysts. *Int J Gynaecol Obstet* 2005;**89**:150–151.

Ferrero S, Arena E, Morando A, Remorgida V. Prevalence of newly diagnosed endometriosis in women attending the general practitioner. *Int J Gynaecol Obstet* 2010;**110**:203–207.

Ferrero S, Venturini PL, Gillott DJ, Remorgida V, Leone Roberti Maggiore U. Hemostasis by bipolar coagulation versus suture after surgical stripping of bilateral ovarian endometriomas: a randomized controlled trial. *J Minim Invasive Gynecol* 2012;**19**:722–730.

Ferrero S, Remorgida V, Venturini PL, Leone Roberti Maggiore U. Norethisterone acetate versus norethisterone acetate combined with letrozole for the treatment of ovarian endometriotic cysts: a patient preference study. *Eur J Obstet Gynecol Reprod Biol* 2014;**174**:117–122.

Ghezzi F, Beretta P, Franchi M, Parissis M, Bolis P. Recurrence of ovarian endometriosis and anatomical location of the primary lesion. *Fertil Steril* 2001;**75**:136–140.

Guerriero S, Ajossa S, Lai MP, Mais V, Paoletti AM, Melis GB. Transvaginal ultrasonography in the diagnosis of pelvic adhesions. *Hum Reprod* 1997;**12**:2649–2653.

Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008;**2**:CD004992. (Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011).

Holland TK, Yazbek J, Cutner A, Saridogan E, Hoo WL, Jurkovic D. Value of transvaginal ultrasound in assessing severity of pelvic endometriosis. *Ultrasound Obstet Gynecol* 2010;**36**:241–248.

Holland TK, Cutner A, Saridogan E, Mavrelos D, Pateman K, Jurkovic D. Ultrasound mapping of pelvic endometriosis: does the location and number of lesions affect the diagnostic accuracy? A multicenter diagnostic accuracy study. *BMC Womens Health* 2013;**13**:43.

Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol* 1986;**67**:335–338.

Jones KD, Sutton CJ. Recurrence of chocolate cysts after laparoscopic ablation. *J Am Assoc Gynecol Laparosc* 2002;**9**:315–320.

Kiran H, Arikan DC, Kaplanoglu M, Bisak U, Cetin MT. Does ovarian endometrioma affect the number of oocytes retrieved for in vitro fertilization? *Bratisl Lek Listy* 2012;**113**:544–547.

Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, Morimoto C, Harada M, Yano T, Taketani Y. Recurrence of ovarian endometrioma after laparoscopic excision. *Hum Reprod* 2006;**21**:2171–2174.

Kumbak B, Kahraman S, Karlikaya G, Lacin S, Guney A. *In vitro* fertilization in normoresponder patients with endometriomas: comparison with basal simple ovarian cysts. *Gynecol Obstet Invest* 2008;**65**:212–216.

Lall Seal S, Kamilya G, Mukherji J, De A, Ghosh D, Majhi AK. Aromatase inhibitors in recurrent ovarian endometriomas: report of five cases with literature review. *Fertil Steril* 2011;**95**:291.e15-8.

Mais V, Guerriero S, Ajossa S, Angiolucci M, Paoletti AM, Melis GB. The efficiency of transvaginal ultrasonography in the diagnosis of endometrioma. *Fertil Steril* 1993;**60**:776–780.

Maneschi F, Marasá L, Incandela S, Mazzarese M, Zupi E. Ovarian cortex surrounding benign neoplasms: a histologic study. *Am J Obstet Gynecol* 1993;**169**:388–393.

Muneyyirci-Delale O, Anopa J, Charles C, Mathur D, Parris R, Cutler JB, Salame G, Abulafia O. Medical management of recurrent endometrioma with long-term norethindrone acetate. *Int J Womens Health* 2012;**4**:149–154.

Muzii L, Bellati F, Bianchi A, Palaia I, Manci N, Zullo MA, Angioli R, Panici PB. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part II: pathological results. *Hum Reprod* 2005;**20**:1987–1992.

Muzii L, Bianchi A, Bellati F, Cristi E, Pernice M, Zullo MA, Angioli R, Panici PB. Histologic analysis of endometriomas: what the surgeon needs to know. *Fertil Steril* 2007;**87**:362–366.

Muzii L, Marana R, Angioli R, Bianchi A, Cucinella G, Vignali M, Benedetti Panici P, Busacca M. Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter? *Fertil Steril* 2011;**95**:2116–2119.

Okaro E, Condous G, Khalid A, Timmerman D, Ameye L, Huffel SV, Bourne T. The use of ultrasound-based 'soft markers' for the prediction of pelvic pathology in women with chronic pelvic pain—can we reduce the need for laparoscopy? *BJOG* 2006;**113**:251–256.

Raffi F, Amer SA. Long-term reproductive performance after surgery for ovarian endometrioma. *Eur J Obstet Gynecol Reprod Biol* 2014;**172**:80–84.

Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2012;**97**:3146–3154.

Raine-Fenning NJ, Clewes JS, Kendall NR, Bunkheila AK, Campbell BK, Johnson IR. The interobserver reliability and validity of volume calculation from three-dimensional ultrasound datasets in the *in vitro* setting. *Ultrasound Obstet Gynecol* 2003;**21**:283–291.

Rana N, Thomas S, Rotman C, Dmowski WP. Decrease in the size of ovarian endometriomas during ovarian suppression in stage IV endometriosis. Role of preoperative medical treatment. *J Reprod Med* 1996;**41**:384–392.

Redwine DB. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999;**72**:310–315.

Reinblatt SL, Ishai L, Shehata F, Son WY, Tulandi T, Almog B. Effects of ovarian endometrioma on embryo quality. *Fertil Steril* 2011;**95**:2700–2702.

Shimizu Y, Takashima A, Takahashi K, Kita N, Fujiwara M, Murakami T. Long-term outcome, including pregnancy rate, recurrence rate and ovarian reserve, after laparoscopic laser ablation surgery in infertile women with endometrioma. *J Obstet Gynaecol Res* 2010;**36**:115–118.

Somigliana E, Berlanda N, Benaglia L, Viganò P, Vercellini P, Fedele L. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications. *Fertil Steril* 2012;**98**:1531–1538.

Suzuki T, Izumi S, Matsubayashi H, Awaji H, Yoshikata K, Makino T. Impact of ovarian endometrioma on oocytes and pregnancy outcome in *in vitro* fertilization. *Fertil Steril* 2005;**83**:908–913.

Tinkanen H, Kujansuu E. *In vitro* fertilization in patients with ovarian endometriomas. *Acta Obstet Gynecol Scand* 2000;**79**:119–122.

Tocci A, Lucchini C, Minasi MG, Greco E. Unilateral ovarian endometriotic cysts do not impair follicles development, oocyte and embryo quality: report on eight controlled ovarian hyperstimulations and ICSI cycles. *Hum Reprod* 2010;**25**:288–289. author reply 289.

Ueda Y, Enomoto T, Miyatake T, Fujita M, Yamamoto R, Kanagawa T, Shimizu H, Kimura T. A retrospective analysis of ovarian endometriosis during pregnancy. *Fertil Steril* 2010;**94**:78–84.

Uncu G, Kasapoglu I, Ozerkan K, Seyhan A, Oral Yilmaztepe A, Ata B. Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve. *Hum Reprod* 2013;**28**:2140–2145.

Vercellini P, Busacca M, Aimi G, Bianchi S, Frontino G, Crosignani PG. Lateral distribution of recurrent ovarian endometriotic cysts. *Fertil Steril* 2002;**77**:848–849.

Yanushpolsky EH, Best CL, Jackson KV, Clarke RN, Barbieri RL, Hornstein MD. Effects of endometriomas on oocyte quality, embryo quality, and pregnancy rates in *in vitro* fertilization cycles: a prospective, case-controlled study. *J Assist Reprod Genet* 1998;**15**:193–197.