Human Reproduction, Vol.24, No.9 pp. 2183–2186, 2009
Advanced Access publication on June 5, 2009 doi:10.1093/humrep/dep202

human reproduction

ORIGINAL ARTICLE *Infertility*

Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation

Laura Benaglia[1,2,3], Edgardo Somigliana[1], Paolo Vercellini[1,2], Annalisa Abbiati[1,2], Guido Ragni[1], and Luigi Fedele[1,2]

[1]Infertility Unit, Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via M. Fanti 6, 20122 Milan, Italy [2]Università degli Studi di Milano, Milan, Italy

[3]Correspondence address. Tel: +39-02-55034303; Fax: +39-02-55034302; E-mail: laurabenaglia@hotmail.it

BACKGROUND: A growing body of evidence suggests that ovarian reserve is damaged after excision of ovarian endometriomas. However, it may not be excluded that gonadal damage is at least partly caused by the very presence of an endometrioma *per se*, thus preceding surgery. To clarify this aspect, we set up a prospective study in women with monolateral endometriomas in order to assess the rate of ovulation in affected ovaries.

MATERIALS AND METHODS: Seventy women with monolateral endometriomas who had not undergone previous adnexal surgery underwent serial ecographic examinations to determine the side of ovulation.

RESULTS: Ovulation occurred in the affected ovary in 22 cases (31%; 95% CI: 22–43%). Assuming that the expected rate of ovulation in both ovaries in healthy women is similar, this difference is statistically significant ($P = 0.002$).

CONCLUSION: The physiological mechanisms leading to ovulation are deranged in ovaries with endometriomas.

Key words: endometriosis / endometrioma / ovulation

Introduction

Endometriosis affects approximately 10% of the female population in their fertile years (Eskenazi *et al*., 2001). Ovarian endometriomas are a common form of the disease and may be present in up to 30–40% of women with endometriosis (Redwine, 1999; Vercellini *et al*., 2006).

A growing body of evidence suggests that ovarian reserve is damaged after excision of ovarian endometriomas (Busacca *et al*., 2006; Gupta *et al*., 2006; Somigliana *et al*., 2006a, 2008; Horikawa *et al*., 2008, Tsoumpou *et al*., 2008; Garcia-Velasco and Somigliana, 2009). The ovulation rate has been repeatedly shown to be reduced in operated gonads compared with contralateral intact gonads (Loh *et al*., 1999; Candiani *et al*., 2005; Horikawa *et al*., 2008). Moreover, data from IVF–ICSI cycles consistently showed a decreased ovarian responsiveness to hyper-stimulation in previously operated ovaries (Ragni *et al*., 2005; Somigliana *et al*., 2006a, 2008; Tsoumpou *et al*., 2008). The damage inflicted by surgery to ovarian reserve may be due to the removal of healthy tissue by laparoscopic stripping, the surgery-related local inflammation or vascular compromise following electrosurgical coagulation (Somigliana *et al*., 2008).

However, it may not be excluded that gonadal damage is at least partly caused by the very presence of an endometrioma *per se*, thus preceeding surgery. Scientific evidence on this issue is extremely scarce. Maneschi *et al*. (1993) found a reduced follicular number and activity antecedent to surgery in ovarian tissue adjacent to endometriomas when compared with teratomas or benign cystadenomas. The functional consequences of this finding have been poorly investigated. In a previous study on women selected for IVF who were found to have unoperated monolateral small endometriomas, we observed a 25% (95% CI; 6–44%) reduction in the number of developing follicles in the affected gonad (Somigliana *et al*., 2006b). However, these women represent a highly selected population and inference of these results to the whole population of women with endometriomas is debatable. Unfortunately, data on natural cycle ovulation in unselected women with ovarian endometriomas is very limited. Recently, Horikawa *et al*. (2008) investigated the rate of ovulation in 28 infertile women with monolateral endometriomas and found a 34% ovulation rate in the affected gonad but the small sample size hampered these authors to provide a statistical validation of this result.

To further clarify this aspect, we set up a larger prospective study in order to assess the rate of ovulation in affected ovaries. To this aim,

women with monolateral endometriomas who had not undergone previous adnexal surgery underwent serial ecographic examinations to determine the side of ovulation.

Materials and Methods

Patients referring to the Department of Obstetrics and Gynecology, Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena for evaluation of adnexal masses, were consecutively considered for inclusion in the study. Women were eligible if they were diagnosed with monolateral ovarian endometrioma(s). Specifically, inclusion criteria were the presence of one or more endometriomas $\geq$10 mm at time of recruitment, no previous adnexal surgery and regularity of menstrual cycles (24–35 days). Women were excluded if they were receiving hormonal treatment such as oral contraceptives, progestins or GnRH analogues and if they reported previous malignancies treated with radio or chemotherapy. The local Institutional Review Board approved the study and all women gave a written informed consent prior to participate.

Selected patients underwent serial transvaginal ultrasounds to determine the side of ovulation starting on day 6–10 of the menstrual cycle. The ovulation was defined as the presence of a growing leading follicle and the subsequent development of an omolateral corpus luteum. Ovarian endometrioma was diagnosed when a round-shaped cystic mass with a minimum diameter of 10 mm, with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes, and without papillary projections was observed (Mais *et al*., 1993). The presence of the endometrioma was always confirmed in at least two ultrasound scans performed at least 2 months apart. The dimension of the cyst was assessed at the time of ovulation monitoring and calculated as the mean of the three perpendicular diameters. All ultrasound tests were performed by two expert technicians (L.B. and E.S.) using the same sonographic instrument (ESAOTE-HITACHI Logos, Genoa, Italy) equipped with a 4–8 MHz (transvaginal) curvilinear probe. A standardized questionnaire aimed to assess endometriosis-related pain symptoms and infertility was used at the time of first ultrasound.

The sample size ($n = 70$) was calculated based on the following assumptions: (1) expected ratio of ovulation in the healthy and affected ovaries: about 1:1 (null hypothesis) (Ecochard and Gougeon, 2000; Rowan *et al*., 2008); (2) clinically relevant difference in the ratio of ovulation in the healthy and affected ovaries: >2:1; and (3) type I and II errors of 0.05 and 0.20, respectively. The combined frequency of the ovulation in the affected and contralateral intact ovaries was analyzed with the χ^2 test to compare observed and expected events. The χ^2 test was calculated using a Tables I and II. A binomial distribution model was used to calculate the 95% Confidence Interval (95% CI) of proportions. *P*-values < 0.05 were considered statistically significant.

Results

Seventy women were recruited. Baseline characteristics of these patients are shown in Table I. Ovulation occurred in the affected ovary in only 22 cases (31%; 95% CI: 22–43%). Assuming that the expected rate of ovulation in both ovaries in healthy women is similar, this difference resulted statistically significant ($P = 0.002$). The impact of the number of endometriomas, their dimension and their side is illustrated in Table II. While the number of the lesions and the side seem to play a role, the dimension does not.

Table I Baseline clinical characteristics of the patients recruited ($n = 70$).

Characteristics	Mean ± SD or number (%)
Age (years)	35.0 ± 4.5
Symptoms	
Dysmenorrhea	45 (64%)
Dyspareunia	21 (30%)
Chronic pelvic pain	24 (34%)
Infertility	36 (51%)
Endometriotic cysts	
1	54 (77%)
2	10 (14%)
3	6 (9%)
Side of the endometrioma	
Right ovary	33 (47%)
Left ovary	37 (53%)
Diameter of the cyst (mm)	31 ± 16
CA-125* (IU/ml)	45.7 ± 31.2

*CA-125, cancer antigen 125.

Discussion

Overall, our results suggest that the presence of an endometrioma has a detrimental impact on ovarian physiology. In fact, the rate of ovulation in healthy and affected ovaries is, respectively, about 2:1. Interestingly, the magnitude of this effect was extremely similar to the one recently reported in the smaller study of Horikawa *et al*. (2008).

Some questions remained unanswered. First, the pathogenic mechanisms leading to this insult are unknown. It may be speculated that the inflammatory reaction typically associated with the presence of endometriosis may play a role. Alternatively, the presence of an expanding ovarian cyst *per se* may mechanically damage the ovarian tissue or disturb the vascularization of the organ. Of note, based on our results, it cannot be inferred that the presence of the endometrioma *per se* is the main cause of the reduced ovulation rate. In fact, this damage may also be consequent to the inflammation surrounding the affected ovary. In this regard, in a rabbit model of endometriosis, Kaplan *et al*. (1989) showed that the endometrial superficial implants in the ovaries decreased the number of ovulation points. This difference was primarily related to peri-ovarian adhesions. In other words, the impaired function of the ovary may be due, at least in part, to other forms of the disease such as superficial implants and adhesions which typically co-exist with ovarian endometriomas. However, the demonstration of a 'gradient' effect in our series supports the role of endometriotic cysts *per se* in the reduction of gonadal function. Indeed, the ovulation rate in the affected ovary was 35% when only one endometrioma was present, and 19% when two or more cysts were detected.

Second, the present study does not disentangle whether the damage is transitory or permanent. The reduction in ovarian function and ovulation rate observed after excision of the cyst may be associated with surgical damage and does not constitute demonstration of a preoperative permanent injury. Of note, the causes determining the

Table II Side of ovulation according to morphological and clinical characteristics.

Characteristics	Number of cases	Ovulation in the affected ovary		
		Number	% (95% CI)	*P*
Entire cohort	70	22	31% (22–43%)	0.002
Number of cysts				
1	54	19	35% (24–49%)	0.028
≥2	16	3	19% (7–43%)	0.012
Dimension of the cysts[a]				
Diameter<30 mm	29	10	34% (20–53%)	0.095
Diameter≥30 mm	25	9	36% (20–56%)	0.162
Side of the cysts				
Right ovary	33	7	21% (11–38%)	<0.001
Left ovary	37	15	41% (26–57%)	0.251

The 95% CI was calculated using a binomial distribution model. *P*-values were calculated using χ^2 test.
[a]Data refers to women with only one endometrioma.

ovulation deficit before and after the removal of the endometrioma may differ.

Final, the observation that damage associated with endometriomas varies according to the affect side is difficult to interpret. It appears that the left ovary is less vulnerable than the right one, as the ovulation rate is significantly reduced only when the cyst is right sided (41 versus 21%). This finding may at least partly explain the repeatedly and consistently demonstrated asymmetry in lateral distribution of ovarian endometriotic cysts (Vercellini *et al*., 1998; Bricou *et al*., 2008). Because ovulation and endometrioma development appear strongly associated (Jain and Dalton, 1999; Vercellini *et al*., 2009) maintenance of ovulatory function in spite of presence of endometriosis may favor cyst formation.

Some limits of the present study should be considered. In particular, patients were recruited only for one cycle. It may be argued that the inclusion of patients for more than one cycle would have been more informative since ovulation is believed to occur alternatively in both ovaries. This decision was taken in order to reduce possible confounding biases. Indeed, we estimated that a study protocol enrolling women for two or even more cycles consecutively would have lead to an elevated proportion of drop-outs, thus introducing possible selection biases. Moreover, some women reported severe pain symptoms and postponing surgery would have been ethically debatable. In this regard, all selected patients in our study accepted to participate and fully adhered to our study protocol. Moreover, it has been demonstrated that, in contrast to common belief, ovulation does not occur alternatively in the two ovaries but this event is independent from the side of ovulation of the preceding cycle (Check *et al*., 1991). Interestingly, six patients in our study requested to be included for more than one cycle and ovulation occurred in the same side for all of them.

A second limit of the study is the absence of an histological confirmation in 17 of the 70 patients recruited. However, many studies have consistently demonstrated the overall accuracy of the non-surgical diagnosis of these cysts with transvaginal ultrasound. Sensitivity and specificity of transvaginal ultrasound have been reported to be 84–100% and 90–100%, respectively (Mais *et al*., 1993; Somigliana *et al*., 2006a). Moreover, our ultrasonographers have vast experience in identifications of endometriotic lesions. In fact, the diagnosis of endometriosis was confirmed in all operated cases in our series ($n = 53$).

In conclusion, the physiological mechanisms leading to ovulation are deranged in ovaries with endometriomas. Further studies are warranted to clarify whether this insult is transitory or permanent.

References

Bricou A, Batt RE, Chapron C. Peritoneal fluid flow influences anatomical distribution of endometriotic lesions: why Sampson seems to be right. *Eur J Obstet Gynecol Reprod Biol* 2008;**138**:127–134.

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.

Candiani M, Barbieri M, Bottani B, Bertulessi C, Vignali M, Agnoli B, Somigliana E, Busacca M. Ovarian recovery after laparoscopic enucleation of ovarian cysts: insights from echographic short-term postsurgical follow-up. *J Minim Invasive Gynecol* 2005;**12**:409–414.

Check JH, Dietterich C, Houck MA. Ipsilateral versus contralateral ovary selection of dominant follicle in succeeding cycle. *Obstet Gynecol* 1991; **77**:247–249.

Ecochard R, Gougeon A. Side of ovulation and cycle characteristics in normally fertile women. *Hum Reprod* 2000;**15**:752–755.

Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P. Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 2001;**76**:929–935.

Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. *Hum Reprod* 2009; **24**:496–501.

Gupta S, Agarwal A, Agarwal R, Loret de Mola JR. Impact of ovarian endometrioma on assisted reproduction outcomes. *Reprod Biomed Online* 2006;**13**:349–360.

Horikawa T, Nakagawa K, Ohgi S, Kojima R, Nakashima A, Ito M, Takahashi Y, Saito H. The frequency of ovulation from the affected ovary decreases following laparoscopic cystectomy in infertile women

with unilateral endometrioma during a natural cycle. *J Assist Reprod Genet* 2008;**25**:239–244.

Jain S, Dalton ME. Chocolate cysts from ovarian follicles. *Fertil Steril* 1999; **72**:852–856.

Kaplan CR, Eddy CA, Olive DL, Schenken RS. Effect of ovarian endometriosis on ovulation in rabbits. *Am J Obstet Gynecol* 1989; **160**:40–44.

Loh FH, Tan AT, Kumar J, Ng SC. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in132 monitored cycles. *Fertil Steril* 1999;**72**:316–321.

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

Ragni G, Somigliana E, Benedetti F, Paffoni A, Vegetti W, Restelli L, Crosignani PG. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: a quantitative rather than a qualitative injury. *Am J Obstet Gynecol* 2005;**19**:1908–1914.

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

Rowan K, Meagher S, Teoh M, Vollenhoven B, Choong S, Tong S. Corpus luteum across the first trimester: size and laterality as observed by ultrasound. *Fertil Steril* 2008;**90**:1844–1847.

Somigliana E, Vercellini P, Vigano P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? *Hum Reprod Update* 2006a;**12**:57–64.

Somigliana E, Infantino M, Benedetti F, Arnoldi M, Calanna G, Ragni G. The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. *Fertil Steril* 2006b;**86**:192–196.

Somigliana E, Arnoldi M, Benaglia L, Iemmello R, Nicolosi AE, Ragni G. IVF-ICSI outcome in women operated on for bilateral endometriomas. *Hum Reprod* 2008;**23**:1526–1530.

Tsoumpou I, Kyrgiou M, Gelbaya TA, Nardo LG. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. *Fertil Steril.* 2008; Aug 8 [Epub ahead of print].

Vercellini P, Aimi G, De Giorgi O, Maddalena S, Carinelli S, Crosignani PG. Is cystic ovarian endometriosis an asymmetric disease? *Br J Obstet Gynaecol* 1998;**105**:1018–1021.

Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D, Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod* 2006;**21**:2679–2685.

Vercellini P, Somigliana E, Viganò P, Abbiati A, Barbara G, Fedele L. 'Blood on the tracks' from corpora lutea to endometriomas. *BJOG* 2009; **116**:366–371.

Submitted on March 27, 2009; resubmitted on May 1, 2009; accepted on May 6, 2009