The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins

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Objective: To clarify whether the presence of ovarian endometriomas is associated with a reduced responsiveness to ovarian hyperstimulation.
Design: Observational study.
Setting: University teaching hospital.
Patient(s): Women selected for in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) cycles who were found to have unilateral ovarian endometriomas and who did not undergo previous ovarian surgery.
Intervention(s): Ovarian hyperstimulation using gonadotropins.
Main Outcome Measure(s): Number of codominant follicles (mean diameter >15 mm) in the affected and in the contralateral intact gonads.
Result(s): Thirty-six patients were enrolled. They underwent 56 IVF-ICSI cycles. The number of codominant follicles in the intact and affected ovaries were 4.0 ± 2.2 and 3.0 ± 1.7, respectively (P=.01). This difference corresponded to a mean reduction (95% confidence interval [CI]) of 25% (6%–44%). This deleterious effect was more evident in women with larger cysts, in those with more than one cyst, and in those who were more responsive to ovarian hyperstimulation.
Conclusion(s): The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. (Fertil Steril® 2006;86:192–6. ©2006 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, endometrioma, IVF, ovarian reserve

The influence of endometriotic ovarian cysts on the results of IVF-ET cycles is a matter of debate. Whereas some studies have documented that ovarian endometriosis is associated with a reduced ovarian reserve (1–9), others failed to observe this association (10–15). Reasons to explain controversies on this issue are presumably multifactorial because IVF outcome can be affected by selection criteria, patient management, stimulation protocols, laboratory procedures, and other factors intrinsic to each institution.

A relevant but poorly considered limit of most studies is that ovarian endometriosis is unilateral in the vast majority of cases (72%–81%) (16–18). The contralateral intact ovary may adequately compensate for the reduced function of the affected gonad (19). Finally, available studies have rarely distinguished between patients who previously underwent surgical treatment of endometriomas and were disease-free at the time of the IVF-ET cycle, those who had endometriomas at the time of the IVF-ET cycle and did not previously undergo ovarian surgery, and those who both had endometriomas at the time of the IVF-ET cycle and previously underwent ovarian surgery. Consequently, it is not possible to discern whether observed effects are consequent to the previous presence of the endometrioma and/or to its surgical treatment.

In recent years, some investigators have highlighted that monitoring the response to ovarian hyperstimulation in women with unilateral disease may be a useful tool to elucidate this point (1, 3, 5, 8, 12, 15). Indeed, comparing follicular development in the affected ovary and using the contralateral intact gonad as a control is a simple and reliable method to assess the influence of an endometrioma and/or its surgical treatment on ovarian function. This study design has been employed by six independent researchers to investigate the effects of surgical treatment of endometriomas (1, 3, 5, 8, 12, 15). Overall, these studies support the view that laparoscopic excision of these cysts is associated with significantly reduced responsiveness to ovarian hyperstimulation. This observation, however, does not clarify whether the damage is consequent to surgery or antecedent to the intervention. Although there are indications to support surgery-mediated damage (14, 20, 21), the possibility that the injury may, at least in part, also precede surgery cannot be excluded.

Clarification of this point is definitely needed, considering that it may have a relevant clinical impact. To shed light on this issue, we have evaluated responsiveness to ovarian hyperstimulation during IVF-ET cycles in women with unilateral endometriomas who did not undergo previous ovarian surgery. Specifically, follicular growth in affected and con-

Received June 7, 2005; revised and accepted December 11, 2005.
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0015-0282/06/$32.00
doi:10.1016/j.fertnstert.2005.12.034

tralateral intact gonads was compared to determine whether the ovarian reserve is already affected before surgery.

MATERIALS AND METHODS

Data from in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) cycles performed at the Infertility Unit of the Department of Obstetrics and Gynecology of the Ospedale Maggiore Policlinico, Mangiagalli, and Regina Elena between January 2000 and December 2004 were reviewed. We included patients who were diagnosed with one or more monolateral endometrioma(s) and who did not undergo previous ovarian surgery. Specifically, inclusion criteria were as follows: [1] women selected for IVF-ICSI cycles, [2] age ≤40 years, [3] ecographic diagnosis of one or more monolateral endometrioma(s), and [4] presence of the endometrioma(s) documented on at least two occasions and at least two menstrual cycles apart. Exclusion criteria were as follows: [1] previous ovarian surgery for endometriomas and/or non-endometriotic benign ovarian cysts, [2] diagnosis of bilateral endometriomas, and [3] cancelled cycles due to hyper or low response.

All patients who referred to the investigators' unit routinely provided an informed consent for their clinical data to be used for research purposes. The local Institutional Review Board approved this study.

Ecographic diagnosis of endometriomas was performed as previously reported (22, 23). Many studies have validated the nonsurgical diagnosis of these cysts with transvaginal ultrasound (14, 22–24). The precise protocol of treatment and ultrasonographic monitoring during the IVF-ICSI cycles employed in our unit is reported elsewhere in further detail (8). In this context, it is of interest that an ultrasound scan was systematically performed on the day of hCG administration (when two or more leading follicles had a mean diameter >18 mm). On this occasion, the number and dimension of all the follicles were recorded. These variables were scheduled separately for the two ovaries. The diameter of the endometriomas and follicles was calculated as the mean of three perpendicular diameters. Codominant follicles were defined as follicles with a mean diameter >15 mm at the time of hCG injection.

Analysis of the data was performed using the Statistics Package for Social Sciences (SPSS 12.0, Chicago, IL). The primary outcome was the number of codominant follicles. This outcome was preferred to the number of oocytes retrieved, considering that the puncture of an endometrioma may sometimes lead to upset infections (25). Consequently, oocyte retrieval is generally performed while trying to avoid puncturing these cysts. Follicle aspiration is thus not always systematic in affected ovaries. Conversely, all follicles are recorded at transvaginal ultrasound. A paired Student's *t*-test was used to investigate the differences between affected and contralateral intact ovaries. The differences were confirmed using a nonparametric Wilcoxon rank test for paired data. A *P* value <.05 was considered statistically significant.

TABLE 1

Characteristics of patients at the time of IVF-ICSI cycle.

Characteristics	Mean ± SD	n (%)
Age (y)	35.2 ± 3.5	
Duration of infertility (y)	4.3 ± 2.2	
BMI (kg/m^2)	21.2 ± 2.4	
FSH day 2–3 of the cycle (mIU/mL)	7.9 ± 2.6	
Endometriomas		
Number		
1		49 (88%)
2		7 (12%)
Side		
Right		17 (30%)
Left		39 (70%)
Diameter (mm)[a]	21 ± 7	
CA-125 (IU/mL)[b]	30 (11–275)	

Note: BMI = body mass index; FSH = follicle-stimulating hormone; CA-125 = cancer antigen 125.

[a] If more than one cyst was diagnosed, the diameter of the larger one is reported.

[b] CA-125 is reported as median (range).

Somigiliana. Endometriomas and ovarian reserve. Fertil Steril 2006.

RESULTS

Thirty-six patients fulfilled our inclusion and exclusion criteria. They underwent 56 IVF-ICSI cycles. Baseline characteristics of patients and cysts are illustrated in Table 1. The median (interquartile range) time between the ecographic diagnosis of the endometrioma and the IVF-ICSI cycle was 10 months (7–18). Nine women subsequently underwent laparoscopic removal of the cysts. The diagnosis of endometriosis was confirmed in all of them. Cycle characteristics and outcomes are listed in Table 2.

The numbers of codominant follicles in the intact and affected ovaries were 4.0 ± 2.2 and 3.0 ± 1.7, respectively (*P*=.01). This difference corresponded to a mean reduction (95% confidence interval [CI]) of 25% (6%–44%). When considering only the first cycle per patient (n = 36), the numbers of codominant follicles in the intact and affected gonads were 4.1 ± 2.2 and 3.2 ± 2.0, respectively (*P*=.09). When considering the successive cycles (n = 20), they were 4.0 ± 2.3 and 2.8 ± 1.2, respectively (*P*=.04).

The data were analyzed according to the characteristics of the endometrioma(s) and the responsiveness to ovarian hyperstimulation (Table 3). This analysis documented that the deleterious effect associated with the presence of the endometrioma(s) was more evident in women with larger cysts, in those with more than one cyst, and in those who were more responsive to ovarian hyperstimulation.