

# Endometrioma $\leq 3$ cm in Diameter per se Does Not Affect Ovarian Reserve in Intracytoplasmic Sperm Injection Cycles

Ibrahim Esinler<sup>a</sup> Gurkan Bozdogan<sup>a</sup> Ilker Arıkan<sup>b</sup> Bulent Demir<sup>c</sup> Hakan Yaralı<sup>a</sup>

<sup>a</sup>Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine, Ankara, <sup>b</sup>Department of Obstetrics and Gynecology, Zonguldak Karaelmas University Faculty of Medicine, Zonguldak, and <sup>c</sup>Department of Obstetrics and Gynecology, Ergani State Hospital, Diyarbakir, Turkey

## Key Words

Endometriosis · Endometrioma · Ovarian reserve · In vitro fertilization · Intracytoplasmic sperm injection

## Abstract

**Background:** Our aim was to determine the effect of single endometriomas  $\leq 3$  cm in diameter per se on ovarian reserve in intracytoplasmic sperm injection (ICSI) cycles. **Methods:** We enrolled 19 consecutive infertile patients (29 cycles) who had unilateral single endometriomas  $\leq 3$  cm in diameter and who underwent ICSI. **Results:** The mean age of the patients was  $33.3 \pm 4.9$  years. The mean diameter of endometriomas was  $21.8 \pm 4.9$  mm. Left- and right-sided endometriomas were 34.5 and 65.5%, respectively. The number of oocytes retrieved from ovaries with endometriomas and contralateral normal ovaries was comparable ( $5.9 \pm 4.3$  vs.  $5.4 \pm 3.8$ ). **Conclusion:** Endometriomas  $\leq 3$  cm in diameter per se did not have a deleterious effect on ovarian reserve in ICSI cycles.

Copyright © 2012 S. Karger AG, Basel

## Introduction

Endometriosis affects about 6–10% of women of reproductive age and is associated with pelvic pain and infertility [1]. Ovarian endometriomas are a common form of the disease and may be present in up to 30–40% of women with endometriosis [2, 3]. Endometrioma cystectomy is the preferred treatment for endometriomas  $>3$  cm in diameter in infertility patients to increase the cumulative pregnancy rates [4, 5]. It may also be performed before in vitro fertilization (IVF) if the diameter of endometrioma is  $>4$  cm [6]. Recently, several clinical studies, including our own [7], have noted the deleterious effect of endometrioma cystectomy on ovarian reserve [8–11]. Inadvertently, removal of primordial follicles during cystectomy, the inflammation process and thermal tissue damage due to bipolar electrocautery usage are the main causative factors for diminished ovarian reserve, but endometrioma per se may also contribute to the decrement in ovarian reserve [12]. Benaglia et al. [13] reported that an ovary with endometrioma was associated with a decreased ovulation rate (31%) when compared to a normal contralateral ovary. However, Almog et al. [14] recently compared the ovarian reserve of ovaries with endometrioma with contralateral normal ovaries in IVF cycles and noted that

an endometrioma per se did not affect the ovarian reserve. Unfortunately, there is no consensus about the effect of endometrioma per se on ovarian reserve in the literature.

Our aim was to determine the effect on endometriomas  $\leq 3$  cm in diameter per se on ovarian reserve in ICSI cycles.

## Patients and Methods

Nineteen consecutive infertile patients (29 cycles) who had unilateral single endometriomas  $\leq 3$  cm in diameter and who underwent intracytoplasmic sperm injection (ICSI) were enrolled retrospectively through our computerized IVF database system. Endometriomas  $>3$  cm in diameter and the patients who had undergone surgery for endometrioma previously or other ovarian cysts were excluded.

Diagnosis of endometrioma was performed by using transvaginal ultrasonography (Logiq 500 Pro; GE Healthcare, Istanbul, Turkey) as described previously [15]. All patients underwent controlled ovarian hyperstimulation consisting of either luteal long GnRH agonist or flexible GnRH antagonist protocol, and recombinant FSH (Gonal-F; Serono, Istanbul, Turkey) using the step-down protocol. When agonists were used, pituitary desensitization was initiated with a daily subcutaneous administration of 1.0 mg leuprolide acetate (Lucrin; Abbott Cedex, Istanbul, Turkey), which began in the luteal phase of the menstrual cycle. This dose was continued until ovarian quiescence was confirmed by vaginal ultrasound following menstruation. When desensitization was achieved, as evidenced by plasma estradiol ( $E_2$ ) levels of  $\leq 50$  pg/ml, the absence of ovarian follicles and endometrial thickness  $\leq 6$  mm on transvaginal ultrasound examination [16], a daily subcutaneous injection of recombinant FSH (Gonal-F; Serono) was commenced. The starting dose of gonadotropin was determined based on female age, antral follicle count at baseline transvaginal ultrasonography, day 3 FSH and  $E_2$  levels, body mass index and previous ovarian response, if available. Ovarian response was monitored with frequent serum  $E_2$  measurements and transvaginal ultrasonography, as described previously [17]. When antagonists were employed, if the serum  $E_2$  level was  $>600$  pg/ml and/or if leading follicles  $>14$  mm in diameter were present, cetrorelix 0.25 mg was initiated as a daily injection up to the day of oocyte pick-up. The criterion for hCG (Profasi or Ovitrelle; Serono) administration was the presence of three or more follicles  $>17$  mm in diameter.

Oocyte retrieval was carried out under local anesthesia using vaginal ultrasound-guided puncture of follicles 36 h after hCG administration. Standard procedures were carried out for gamete-embryo handling and embryo transfer was performed under abdominal ultrasonography guidance in all cases using a soft catheter (Wallace; PM Group, Istanbul, Turkey). The luteal phase was supported by daily vaginal progesterone suppositories (Crinone; Serono) starting 1 day after oocyte pick-up. Clinical pregnancy was defined as the presence of an intrauterine gestational sac by transvaginal ultrasonography.

The statistical analyses were performed using Statistics Package for Social Sciences version 17.0 (SPSS, Inc., Chicago, Ill., USA). The comparison of the number of oocyte-cumulus complexes re-

**Table 1.** Baseline characteristics of patients with unilateral endometrioma

Patients, n	19
Cycles, n	29
Cancelled cycles, n (%)	1 (3.4)
Female age, years	33.3 $\pm$ 4.9
Body mass index	23.7 $\pm$ 3.6
Duration of infertility, months	77.7 $\pm$ 74.6
Side of endometrioma	
Right ovary, n (%)	10 (34.5)
Left ovary, n (%)	19 (65.5)
Diameter of endometrioma, mm	21.8 $\pm$ 4.9

**Table 2.** Antral follicle count, oocytes retrieved, MII oocyte and fertilization rate for affected ovary and contralateral normal ovary

Variable	Ovary containing endometrioma (n = 28)	Contralateral normal ovary (n = 28)	p value
Antral follicle count, n	5.0 $\pm$ 4.1	4.7 $\pm$ 3.9	NS
Oocytes retrieved, n	5.9 $\pm$ 4.3	5.4 $\pm$ 3.8	NS
MIII oocytes, n	4.1 $\pm$ 3.9	3.9 $\pm$ 2.8	NS
Fertilization rate, %	70.8	71.4	NS

trieved from ovaries with endometrioma and contralateral normal ovaries was performed by use of paired sample t test. p values of  $<0.05$  were considered statistically significant. Values were expressed as mean  $\pm$  SD, unless stated otherwise.

## Results

The baseline characteristics of patients are shown in table 1. The mean age of the patients was 33.3  $\pm$  4.9 years. The mean diameter of endometriomas was 21.8  $\pm$  4.9 mm. Left- and right-sided endometriomas were 34.5 and 65.5%, respectively. The number of oocytes retrieved in ovaries with endometrioma and contralateral normal ovaries was comparable (5.9  $\pm$  4.3 vs. 5.4  $\pm$  3.8) (table 2). The clinical pregnancy rate was 42.9%.

## Discussion

There is growing consensus about the deleterious effect of endometrioma cystectomy on ovarian reserve [7–11]. Inadvertently, removal of primordial follicles during

cystectomy, the inflammation process and thermal tissue damage due to bipolar electrocautery usage are the main causative factors for diminished ovarian reserve. It is hypothesized that endometrioma per se may also contribute to the diminishment of ovarian reserve. However, there is paucity of data on the effect of endometrioma per se on ovarian reserve in the literature. Maneschi et al. [18] found a reduced presence of healthy ovarian tissue in cortex harvested from ovaries with endometriomas ( $6.5 \pm 2.3$  cm) compared with other similar-sized benign ovarian cysts by semiquantitative scoring. Kitajima et al. [19] recently analyzed 20 samples of cortical tissue from ovaries with endometriomas ( $\leq 4$  cm) and 11 samples from contralateral ovaries without cysts. Follicular density was significantly lower in the cortex of ovaries with endometriomas than in the cortex from contralateral ovaries without cysts ( $6.3 \pm 4.1$  vs.  $25.1 \pm 15.0/\text{mm}^3$ ). Eleven (55%) cortical samples from ovaries with endometriomas showed fibrosis and concomitant loss of cortex-specific stroma, not observed in contralateral normal ovaries. Multivariate analysis revealed that the presence of endometriomas and fibrosis were significantly and independently associated with follicular density.

At least two hypotheses may explain the deleterious effect of endometrioma per se on ovarian reserve. One is that simple mechanical tissue stretching by large cysts might be responsible for reduced follicular density in the cortex surrounding endometriomas. Another hypothesis suggests that oxidative stress induces ovarian tissue damage and oocyte apoptosis [20]. Matsuzaki and Schubert [21] demonstrated that the normal ovarian cortex surrounding endometriotic tissues was affected more severely by oxidative stress than the ovarian cortex surrounding other benign ovarian cysts.

In addition to histopathological studies [18, 19, 21], Benaglia et al. [13] investigated 70 women with monolateral endometriomas who had not undergone previous adnexal surgery in their clinical study. They noted that spontaneous ovulation occurred in the affected ovary (mean diameter of endometrioma  $31 \pm 16$  mm) in 22 cases (31%; 95% confidence interval 22–43). Assuming that the expected rate of ovulation in both ovaries in healthy women is similar, this difference was statistically significant ( $p < 0.05$ ).

Somigliana et al. [22] enrolled 36 patients (56 cycles) with unilateral endometrioma who underwent IVF-ICSI. The number of co-dominant follicles in the intact and affected ovaries was  $4.0 \pm 2.2$  and  $3.0 \pm 1.7$ , respectively ( $p < 0.01$ ). This difference corresponded to a mean reduction (25%; 95% confidence interval 6–44). However, the

same authors [23] recently investigated the effect of non-operated unilateral endometrioma ( $21 \pm 8$  mm) on ovarian reserve in IVF cycles and failed to find an association. They noted that the median IQR of the total number of follicles (diameter  $\geq 11$  mm) in the affected and intact ovaries was 5 (3–7) and 5 (3–8), respectively ( $p > 0.05$ ). Considering the co-dominant follicles (diameter  $> 15$  mm), the median (IQR) number in the affected and intact ovaries was 3 (2–4) and 3 (2–5), respectively ( $p > 0.05$ ). Almog et al. [14] recently enrolled 81 patients with unilateral endometrioma ( $28.4 \pm 3.9$  mm) and compared the number of oocytes retrieved in ovaries with endometrioma to those of contralateral normal ovaries. They reported that there was no significant difference in the number of antral follicles and oocytes retrieved in the endometrioma-containing ovary ( $6.0 \pm 0.4$  and  $7.7 \pm 1.0$ , respectively) and in the opposite ovary ( $6.1 \pm 0.5$  and  $8.5 \pm 0.9$ , respectively). Furthermore, there was no correlation between the size and the number of endometriomas with the number of retrieved oocytes.

Our results support two recently published studies [14, 23]. We noted that affected ovaries produced a similar number of oocytes as contralateral normal ovaries ( $5.9 \pm 4.3$  vs.  $5.4 \pm 3.8$ ) in ICSI cycles. The mean diameter of endometriomas was  $28.4 \pm 3.9$  and  $21 \pm 8$  mm in the studies by Almog et al. [14] and Benaglia et al. [23], respectively. The respective figure was  $21.8 \pm 4.9$  mm in our study. In our IVF center, endometriomas  $\geq 4$  cm in diameter usually undergo cystectomy before IVF. Therefore, studies investigating the effect of endometriomas  $> 4$  cm per se on ovarian reserve in IVF cycles are needed. There is to our knowledge no study with such a design in the literature. Although histopathological studies [18, 19, 21] and studies in which the endpoint was spontaneous ovulation [13] showed an association with endometrioma per se with diminished ovarian reserve, this deleterious effect did not seem to be reflected when controlled ovarian hyperstimulation was employed. The main limitation of our study is its small sample size (19 patients, 29 cycles). Since the sample size is small, we could not run a power analysis. Further studies with a larger sample size are therefore needed.

In conclusion, a single endometrioma  $\leq 3$  cm in diameter per se did not have a deleterious effect on ovarian reserve in ICSI cycles. It is therefore logical not to touch single endometriomas  $\leq 3$  cm in diameter before IVF.

#### Disclosure Statement

The authors have no conflicts of interest to disclose.

## References

- 1 Giudice LC, Kao LC: Endometriosis. *Lancet* 2004;364:1789–1799.
- 2 Redwine DB: Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. *Fertil Steril* 1999;72:310–315.
- 3 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.
- 4 Alborzi S, Momtahan M, Parsanezhad ME, Dehbashi S, Zolghadri J: A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril* 2004;82:1633–1637.
- 5 Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P: Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril* 1998;70:1176–1180.
- 6 Falcone T, Lebovic DI: Clinical management of endometriosis. *Obstet Gynecol* 2011;118:691–705.
- 7 Esinler I, Bozdag G, Aybar F, Bayar U, Yarali H: Outcome of in vitro fertilization/intracytoplasmic sperm injection after laparoscopic cystectomy for endometriomas. *Fertil Steril* 2006;85:1730–1735.
- 8 Almog B, Sheizaf B, Shalom-Paz E, Shehata F, Al-Talib A, Tulandi T: Effects of excision of ovarian endometrioma on the antral follicle count and collected oocytes for in vitro fertilization. *Fertil Steril* 2010;94:2340–2342.
- 9 Duru NK, Dede M, Acikel CH, Keskin U, Fidan U, Baser I: Outcome of in vitro fertilization and ovarian response after endometrioma stripping at laparoscopy and laparotomy. *J Reprod Med* 2007;52:805–809.
- 10 Ercan CM, Duru NK, Karasahin KE, Coksuer H, Dede M, Baser I: Ultrasonographic evaluation and anti-müllerian hormone levels after laparoscopic stripping of unilateral endometriomas. *Eur J Obstet Gynecol Reprod Bio* 2011;158:280–284.
- 11 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;193:1908–1914.
- 12 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.
- 13 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.
- 14 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.
- 15 Alcazar JL, Laparte C, Jurado M, Lopez-Garcia G: The role of transvaginal ultrasonography combined with color velocity imaging and pulsed Doppler in the diagnosis of endometrioma. *Fertil Steril* 1997;67:487–491.
- 16 Barash A, Weissman A, Manor M, Milman D, Ben-Arie A, Shoham Z: Prospective evaluation of endometrial thickness as a predictor of pituitary down-regulation after gonadotropin-releasing hormone analogue administration in an in vitro fertilization program. *Fertil Steril* 1998;69:496–499.
- 17 Bukulmez O, Yarali H, Yucel A, Sari T, Gurgan T: Intracytoplasmic sperm injection versus in vitro fertilization for patients with a tubal factor as their sole cause of infertility: a prospective, randomized trial. *Fertil Steril* 2000;73:38–42.
- 18 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.
- 19 Kitajima M, Defrere S, Dolmans MM, Colette S, Squifflet J, Van Langendonck A, Donnez J: Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. *Fertil Steril* 2011;96:685–691.
- 20 Zhang X, Li XH, Ma X, Wang ZH, Lu S, Guo YL: Redox-induced apoptosis of human oocytes in resting follicles in vitro. *J Soc Gynecol Invest* 2006;13:451–458.
- 21 Matsuzaki S, Schubert B: Oxidative stress status in normal ovarian cortex surrounding ovarian endometriosis. *Fertil Steril* 2010;93:2431–2432.
- 22 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* 2006;86:192–196.
- 23 Benaglia L, Pasin R, Somigliana E, Vercellini P, Ragni G, Fedele L: Unoperated ovarian endometriomas and responsiveness to hyperstimulation. *Hum Reprod* 2011;26:1356–1361.