

# Ovarian response during IVF–embryo transfer cycles after laparoscopic ovarian cystectomy for endometriotic cysts of >3 cm in diameter

M.Canis<sup>1</sup>, J.L.Pouly, S.Tamburro, G.Mage, A.Wattiez and M.A.Bruhat

Department of Obstetrics, Gynaecology and Reproductive Medicine, CHU Bd. Leon Malfreyt 63058 Clermont Ferrand, Cedex 1 France

<sup>1</sup>To whom correspondence should be addressed. E-mail: mcanis@chu-clermontferrand.fr

**BACKGROUND:** Ovarian response during IVF cycles after laparoscopic ovarian cystectomy for endometriotic cysts >3 cm is controversial. A retrospective study was designed to study this problem. **METHODS:** At laparoscopy, endometriomas >3 cm were treated by ovarian cystectomy, whilst adhesions and peritoneal endometriosis were treated using conventional techniques. Ovarian stimulation was achieved with clomiphene and gonadotrophins or with gonadotrophins after a desensitization with gonadotrophin-releasing hormone agonists. Three groups of patients were retrospectively selected from an IVF–embryo transfer database: patients who underwent laparoscopic ovarian cystectomy for an endometrioma >3 cm (Group A,  $n = 41$ ), patients with endometriosis without ovarian endometrioma (Group B,  $n = 139$ ) and patients with tubal infertility (Group C,  $n = 59$ ). **RESULTS:** The groups did not differ in age. In the first IVF cycle, the mean ( $\pm$  SD) numbers of oocytes and of embryos were  $9.4 \pm 6.2$  and  $4.7 \pm 3.6$  respectively in group A and  $11.6 \pm 7.5$  and  $5.1 \pm 4.9$  in group B (not significant). The results did not differ in cycles 2 and 3 or when compared according to age. No difference was found when comparing patients with endometriosis and patients with tubal infertility. **CONCLUSION:** The number of oocytes and embryos obtained was not significantly decreased by laparoscopic cystectomy, suggesting that in experienced hands this procedure may be a valuable surgical tool for the treatment of large ovarian endometriomas. However, great care must be taken to avoid ovarian damage.

*Key words:* cystectomy/endometriosis/IVF–embryo transfer/laparoscopy/ovary

## Introduction

Laparoscopic surgery has become the gold standard for the treatment of ovarian endometriomas (Daniel *et al.*, 1991; Canis *et al.*, 1995; Donnez *et al.*, 1996; Sutton *et al.*, 1997). Three laparoscopic techniques have been proposed for the management of endometriomas of >3 cm in diameter. Donnez *et al.* and Brossens *et al.* proposed a three-step treatment which involves the laparoscopic drainage of the cyst, 3 months medical treatment with gonadotrophin releasing hormone (GnRH) analogues and a second laparoscopic procedure to achieve a laser vaporization of the remaining endometriotic implants inside the cyst (Brossens *et al.*, 1996; Donnez *et al.*, 1996). Sutton *et al.* proposed a laser vaporization of the cyst wall without pre-operative medical treatment in cysts of <10 cm in diameter (Sutton *et al.*, 1997). We, and others, have described a laparoscopic ovarian cystectomy using a stripping technique modified from that used to treat benign ovarian neoplasms (Reich and McGlynn, 1986; Canis *et al.*, 1992).

Controversial data were reported on the consequences of laparoscopic cystectomy on ovarian response during ovarian

stimulation during IVF treatment; Williams *et al.* reported a deleterious effect of previous ovarian surgery, which was not confirmed by Loh *et al.* (Williams *et al.*, 1998; Loh *et al.*, 1999).

In the present study, we compared the number of oocytes and embryos obtained from IVF–embryo transfer cycles in patients treated by cystectomy for an endometrioma >3 cm with the numbers obtained from patients treated by laparoscopy for pelvic endometriosis, but without deep ovarian endometriosis.

## Materials and methods

Patients were retrospectively selected from our IVF–embryo transfer database. We included patients with infertility-associated endometriosis who underwent laparoscopic surgery and all IVF cycles carried out in our department. Three groups of patients were selected. In group A, we included 41 patients who had a laparoscopic ovarian cystectomy for an ovarian endometrioma of >3 cm in diameter; 30 patients had a unilateral endometrioma >3 cm and 11 had bilateral endometriomas, including six patients treated for two endometriomas >3 cm. In group B, we included 139 patients treated laparoscopically for endometriosis, but without deep ovarian endometriosis. Cycles

**Table I.** Comparison of groups A and B

	Group A (endometrioma >3 cm)	Group B (no endometrioma)
<i>n</i>	41	139
Age	30.3 ± 4.0	31.0 ± 4.1
rAFS score (The American Fertility Society, 1985)	70.0 ± 35.4	10.6 ± 16.9
rAFS stage III–IV	41 (100%)	24 (17.3%)
Male infertility	17 (41.4%)	59 (42.4%)
Previous treatment for endometriosis	19 (46.3%)	12 (8.6%)
Previous surgical treatment for endometriosis	17 (41.5%)	6 (4.3%)
Post-operative medical treatment	29 (70.7%)	28 (20.1%)
Delay before IVF (months)	14.5 ± 14.4	16.0 ± 11.9
IVF cycle 1		
Number of cases	39	136
GnRH long protocol (cycle 1)	29 (74.4%)	98 (72.1%)

Values are mean ± SD.

were excluded if the oocyte retrieval was performed by laparoscopy. Gamete intra-Fallopian transfer (GIFT), zygote intra-Fallopian transfer (ZIFT) and intracytoplasmic sperm injection (ICSI) cycles were also excluded. Patients who underwent GIFT, ZIFT or ICSI for one cycle and IVF for the other cycles were included in the study, but only their IVF cycles were taken into account. Consequently, only 39 and 128 patients were included in cycle 1.

At laparoscopy the endometriosis was staged according to the revised American Fertility Society (rAFS) classification scheme (The American Fertility Society, 1985). The technique used for the laparoscopic treatment has been reported previously (Canis *et al.*, 1995). Peritoneal endometriosis was treated according to its location and the patient's clinical symptoms. Patients with severe pain and deep infiltrating disease were treated with surgical excision, whereas patients with superficial peritoneal disease were treated with bipolar coagulation and/or CO<sub>2</sub> laser vaporization. Ovarian endometriomas >3 cm were treated using a stripping technique (Canis *et al.*, 1995). The post-operative management of endometriosis-associated infertility was as follows: patients with extensive endometriosis, male infertility, a duration of infertility >8 years and who were >38 years old were included in our IVF programme immediately after the laparoscopic treatment and 3 months treatment with GnRH analogues. The other patients were referred to IVF when not pregnant 9–12 months after the laparoscopic procedure.

The third and final group consisted of 59 patients with tubal infertility who underwent IVF in our department between January 1993 and December 1996 using a GnRH long protocol. The patients were retrospectively selected from our database (group C), after excluding an associated male factor and/or ovulation disorders.

Statistical analysis was performed using the statistical program Stat View (Abacus concept Inc., Berkeley, CA, USA). Fisher's exact,  $\chi^2$  and Student's *t*-tests were used to compare the groups included in the study. A Mann–Whitney *U*-test was applied to compare the number of oocytes and embryos.

## Results

The endometriosis groups (groups A and B) are compared in Table I. The mean age of the patients, the mean delay between laparoscopy and IVF, and the incidence of male infertility were similar, whereas the mean rAFS score and the incidence of previous surgical treatment and of post-operative medical treatment were significantly higher in group A. The ovarian stimulation regimens were similar in both groups (Table I).

The mean age of patients with tubal infertility was  $32.1 \pm 5.1$  years, which was not significantly different from either of the endometriosis groups.

The mean number of oocytes and embryos obtained in each group are presented in Table II. There were no significant differences between groups A, B or C.

Data from the first IVF cycle were used to compare the results obtained according to age, ovarian stimulation regimen and the number of cysts treated. In patients <35 years old, the number of oocytes and embryos were respectively  $9.9 \pm 6.4$  and  $5.0 \pm 5.1$  in group A ( $n = 35$ ), and  $12.1 \pm 8.0$  and  $5.2 \pm 5.2$  in group B ( $n = 99$ ) (not significant). In patients who received a long GnRH protocol, the number of oocytes and embryos were respectively  $10.1 \pm 6.6$  and  $5.0 \pm 3.9$  in group A ( $n = 29$ ), and  $12.3 \pm 7.8$  and  $5.4 \pm 5.1$  in group B ( $n = 95$ ) (not significant). In the first IVF cycle, the mean number of oocytes and embryos was respectively  $7.9 \pm 4.7$  and  $3.9 \pm 2.4$  in patients treated for 2 ovarian endometriomas ( $n = 11$ ),  $10.0 \pm 6.7$  and  $5.0 \pm 4.0$  in patients treated for one ovarian endometrioma ( $n = 28$ ), and  $11.6 \pm 7.5$  and  $5.1 \pm 4.9$  in patients without endometriomas ( $n = 128$ ) (not significant).

The pregnancy rates (clinical pregnancies/oocyte retrieval) obtained in groups A, B and C are shown in Table III.

## Discussion

The surgical treatment of large ovarian endometriomas is controversial. According to Donnez *et al.* and Brosens *et al.* the cyst should be treated by laser vaporization after a pre-operative medical treatment, whereas Sutton *et al.* proposed a laser vaporization without pre-operative medical treatment (Brosens *et al.*, 1996; Donnez *et al.*, 1996; Sutton *et al.*, 1997). These techniques were proposed according to the theory of Hughesdon, who suggested that ovarian endometrioma originated from the invagination of the ovarian cortex induced by the progression of endometriotic implants trapped by adhesions on the surface of the ovary (Hughesdon, 1957). Nisolle and Donnez proposed a different mechanism, with the endometrioma invaginated in the ovary being induced by metaplasia of the ovarian epithelium (Nisolle and Donnez,

**Table II.** Number of oocytes and embryos obtained from patients with endometriosis\*

	Group A (endometrioma >3 cm)			Group B (no endometrioma)			Group C (tubal infertility)		
	<i>n</i>	Oocytes	Embryos	<i>n</i>	Oocytes	Embryos	<i>n</i>	Oocytes	Embryos
Cycle 1	39	9.4 ± 6.2	4.7 ± 3.6	128	11.6 ± 7.5	5.1 ± 4.9	59	10.9 ± 6.5	5.8 ± 4.9
Cycle 2	17	9.2 ± 5.7	4.9 ± 3.2	80	11.2 ± 8.0	4.5 ± 4.9	37	10.9 ± 6.8	5.0 ± 3.9
Cycle 3	11	10.9 ± 6.1	4.5 ± 4.3	44	11.2 ± 8.1	4.7 ± 3.9	18	10.4 ± 7.7	4.1 ± 3.5
Cycle >3	7	8.6 ± 2.9	4.2 ± 3.3	51	8.7 ± 5.6	4.3 ± 4.0	13	8.0 ± 3.7	4.0 ± 2.3

\*No significant difference was found when comparing the results obtained in the groups.  
Values are mean ± SD.

**Table III.** Pregnancy rates (clinical pregnancy/oocyte retrieval)

	Group A (endometrioma >3 cm)		Group B (no endometrioma)		Group C (tubal infertility)	
	<i>n</i>	IUP <i>n</i> (%)	<i>n</i>	IUP <i>n</i> (%)	<i>n</i>	IUP <i>n</i> (%)
Cycle 1	39	14 (35.9)	128	40 (31.2)	59	18 (30.5)
Cycle 2	17	6 (33.3)	80	22 (27.5)	37	9 (24.3)
Cycle 3	11	2 (18.5)	44	12 (27.3)	18	2 (11.1)
Cycle >3	7	0	51	12 (23.5)	13	3 (23.1)

IUP = intra-uterine pregnancy.

1997). According to these theories, the disease is external to the ovary, so that cystectomy appears as an over-treatment which may lead to unnecessary ovarian damage. In contrast, we, and others, have reported the treatment of ovarian endometrioma by ovarian cystectomy using a stripping technique with minimal complications and pregnancy rates similar to those reported when endometriosis was treated using microsurgery by laparotomy (Gordts *et al.*, 1984; Canis *et al.*, 1995).

The results reported here demonstrate that the number of oocytes retrieved after ovarian stimulation during an IVF cycle was similar in patients who underwent prior cystectomy and in patients with endometriosis without deep ovarian endometriosis. Moreover, the number of embryos and the pregnancy rates were not different. Loh *et al.* reported similar results after flare-down regimens, although they found a decreased follicular response in spontaneous and clomiphene-stimulated cycles (Loh *et al.*, 1999). Other studies have suggested that cystectomy may induce a loss of follicle reserve and a decreased number of oocytes retrieved during IVF cycles (Muruyama *et al.*, 1996; Chang *et al.*, 1998; Williams *et al.*, 1998). However in these studies, the results were not reported according to the surgical technique, i.e. laparoscopy or laparotomy, cystectomy or laser vaporization. In contrast, Beretta *et al.* reported better pregnancy rates after laparoscopic ovarian cystectomy than after drainage and coagulation performed with bipolar coagulation (Beretta *et al.*, 1998). Recently, similar numbers of oocytes have been found in patients treated by ovarian cystectomy and by laser vaporization (J.Donnez, personal communication). Hemmings *et al.* reported similar pregnancy rates after fenestration and coagulation to those obtained after ovarian cystectomy, although fenestration and coagulation led to a faster conception (Hemmings *et al.*, 1998).

When compared with CO<sub>2</sub> laser vaporization, ovarian cystectomy has several advantages. Treatment can be performed in one surgical procedure using conventional laparoscopic instruments available in most endoscopic departments. It allows a complete pathological examination of the cyst wall. Moreover, Saleh and Tulandi reported an 18 month re-operation rate of 6.1% after cystectomy compared with 21.9% after fenestration and ablation (Saleh and Tulandi, 1999).

From our results and these data from the literature, laparoscopic ovarian cystectomy appears to be a valuable surgical technique in the treatment of ovarian endometriomas >3 cm. However, it should be emphasized that the technique should be different from that used in the treatment of benign ovarian neoplasm. The reason is that the cyst lining is surrounded by fibrosis, which makes cleavage more difficult (Donnez *et al.*, 1996). Therefore, the treatment of a large endometrioma should comprise the following steps. Step 1: peritoneal cytology and inspection of the peritoneal cavity should be performed to exclude malignancy. Step 2: the ovary is freed from the broad ligament, the endometrioma almost invariably ruptures, a careful lavage is performed. Step 3: endocystic examination excludes any signs of malignancy. Step 4: to identify the cleavage plane the ovarian incision is enlarged. Step 5: the initial part of the dissection is easy using two grasping forceps. Step 6: cleavage becomes more difficult, with red fibrotic tissue visible on the surface of the cyst wall. The stripping technique would remove the fibrosis, and induce bleeding and severe thermal damage to the ovary. Step 7: to avoid this complication, the plane is exposed with two grasping forceps, the red fibrotic fibres on the surface of the cyst are coagulated and cut to identify the cleavage plane close to the cyst wall. Step 8: haemostasis is achieved with bipolar coagulation. One

intra-ovarian suture is used if the shape of the ovary is not approximated spontaneously. Step 9: the cyst wall is extracted using an endobag (Karl Storz, Tuttingen, Germany).

As dissection generally becomes difficult close to the ovarian hilum, an inadequate technique may tear ovarian vessels and induce significant ovarian damage. This should be avoided using a careful technique and following all the principles of microsurgery. If dissection appears too difficult and/or if the endometrioma is >8 cm in diameter, it may be better to stop the procedure and to use the three-step procedure suggested by Donnez *et al.* (Donnez *et al.*, 1996) or to coagulate the remaining cyst lining, if small. Although Muzii *et al.* demonstrated that a pre-operative medical treatment does not facilitate surgical treatment (Muzii *et al.*, 1996), we use this type of management for very large endometriomas to decrease the diameter of the cyst as suggested by Donnez *et al.* (Donnez *et al.*, 1994).

Although not statistically significant, the lower number of oocytes obtained in patients with bilateral ovarian endometriomas, and the results from Loh *et al.* in spontaneous and clomiphene-stimulated cycles, suggested that ovarian response may be impaired in patients treated for large deep ovarian endometriomas (Loh *et al.*, 1999). However, the decreased ovarian response may not be related to the surgical procedure. Using pathological sections of the ovarian cortex surrounding ovarian endometriomas, Maneschi *et al.* found a reduced number of follicles and vascular activity before any surgical procedure, suggesting that the disease may damage the ovary (Maneschi *et al.*, 1993). Moreover, Kaplan *et al.* showed in a rabbit model that endometrial implants in the ovaries decreased the number of ovulation points when compared with adipose tissue (Kaplan *et al.*, 1989). This difference was primarily related to peri-ovarian adhesions. Therefore, the decreased ovarian response, which may be observed in patients previously treated for a large ovarian endometrioma, may also be a consequence of the disease. This hypothesis needs to be taken into account when proposing non-surgical management of these patients.

Controversial results concerning ovarian endometriosis and IVF-embryo transfer were recently reported (Isaacs *et al.*, 1997; Nakahara *et al.*, 1998; Al-Azemi *et al.*, 2000; Tinkanen and Kujansuu, 2000). When patients with an ovarian endometrioma, aspirated at the time of oocyte retrieval, were compared with patients who had only peritoneal endometriosis, no difference was found, whereas when patients with ovarian involvement were compared with patients with tubal or male factors, a decreased ovarian response was found, although similar pregnancy rates were obtained. In the present study, we found no difference when comparing patients with endometriosis and with tubal infertility.

Our data strongly suggest that in experienced hands laparoscopic ovarian cystectomy for large endometriomas is valuable. However, a very cautious technique should be used to avoid ovarian damage. Prospective studies of infertile patients with ovarian endometriomas are now necessary to establish the best management of ovarian endometriomas in IVF patients.

## References

- Al-Azemi, M., Bernal, A.L., Steele, J. *et al.* (2000) Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis. *Hum. Reprod.*, **15**, 72–75.
- Beretta, P., Franchi, M., Ghezzi, F. *et al.* (1998) Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil. Steril.*, **70**, 1176–1180.
- Brosens, I.A., Van Ballaer, P., Puttemans, P. *et al.* (1996) Reconstruction of the ovary containing large endometriomas by an extraovarian endoscopic technique. *Fertil. Steril.*, **66**, 517–521.
- Canis, M., Mage, G., Wattiez, A. *et al.* (1992) Second-look laparoscopy after laparoscopic cystectomy of large ovarian endometriomas. *Fertil. Steril.*, **58**, 617–619.
- Canis, M., Boughizane, S., Loh, F.H. *et al.* (1995) Techniques for ablation and excision of endometriosis. In Shaw, R.D. (ed.) *Endometriosis current understanding and management*. Blackwell Science, Oxford, pp. 248–263.
- Chang, M.Y., Chiang, C.H., Hou, H.C. *et al.* (1998) The outcome of assisted reproductive therapies in patients with endometriosis is affected by antral follicle count and previous endometrioma surgeries. *Proceedings of the Sixth world congress on endometriosis; 1998 June 30-July 4; Quebec City, Quebec, Canada*, p180.
- Daniell, J.F., Kurtz, B.R. and Gurley, L.D. (1991) Laser laparoscopic management of large endometriomas. *Fertil. Steril.*, **55**, 692–695.
- Donnez, J., Nisolle, M., Gillerot, S. *et al.* (1994) Ovarian endometrial cysts: the role of gonadotropin-releasing hormone agonist and/or drainage. *Fertil. Steril.*, **62**, 63–66.
- Donnez, J., Nisolle, M., Gillet, N. *et al.* (1996) Large ovarian endometriomas. *Hum. Reprod.*, **11**, 641–646.
- Gordts, S., Boeckx, W. and Brosens, I. (1984) Microsurgery of endometriosis in infertile patients. *Fertil. Steril.*, **42**, 520–525.
- Hemmings, R., Bissonnette, F. and Bouzayen, R. (1998) Results of laparoscopic treatments of ovarian endometriomas: laparoscopic ovarian fenestration and coagulation. *Fertil. Steril.*, **70**, 527–529.
- Hughesdon, P.E. (1957) The structure of endometrial cyst of the ovary. *J. Obstet. Gynecol. Br. Emp.*, **44**, 481–487.
- Isaacs, J.D., Hines, R.S., Sopelak, V.M. *et al.* (1997) Ovarian endometriomas do not adversely affect pregnancy success following in vitro fertilization. *J. Assist. Reprod. Genet.*, **14**, 551–553.
- Kaplan, C.R., Eddy, C.A., Olive, D.L. *et al.* (1989) Effect of ovarian endometriosis on ovulation in rabbits. *Am. J. Obstet. Gynecol.*, **160**, 40–44.
- Loh, F.H., Tan, A.T., Kumar, J. *et al.* (1999) Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. *Fertil. Steril.*, **72**, 316–321.
- Maneschi, F., Marasa, L., Incandela, S. *et al.* (1993) Ovarian cortex surrounding benign neoplasms: a histologic study. *Am. J. Obstet. Gynecol.*, **169**, 388–393.
- Muruyama, M., Yano, T., Morita, Y. *et al.* (1996) Effect of ovarian cystectomy on outcome of IVF-embryo transfer treatment in endometriosis patients. *Proceedings of the Fifth World Congress on Endometriosis October 21–24, Yokohama Yokohama, je crois, Japan*, p 144.
- Muzii, L., Marana, R., Caruana, P. *et al.* (1996) The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. *Fertil. Steril.*, **65**, 1235–1237.
- Nakahara, K., Saito, H., Saito, T. *et al.* (1998) Ovarian fecundity in patients with endometriosis can be estimated by the incidence of apoptotic bodies. *Fertil. Steril.*, **69**, 931–935.
- Nisolle, M. and Donnez, J. (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil. Steril.*, **68**, 585–596.
- Reich, H. and McGlynn, F. (1986) Treatment of ovarian endometriomas using laparoscopic surgical techniques. *J. Reprod. Med.*, **31**, 577–584.
- Saleh, A. and Tulandi, T. (1999) Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. *Fertil. Steril.*, **72**, 322–324.
- Sutton, C.J., Ewen, S.P., Jacobs, S.A. and Whitelaw, N.L. (1997) Laser laparoscopic surgery in the treatment of ovarian endometriomas. *J. Am. Assoc. Gynecol. Laparosc.*, **4**, 319–323.
- The American Fertility Society (1985) Revised American Fertility Society Classification of endometriosis: 1985. *Fertil. Steril.*, **43**, 351–352.
- Tinkanen, H. and Kujansuu, E. (2000) In vitro fertilization in patients with ovarian endometriosis. *Acta. Obstet. Gynaecol. Scand.*, **79**, 119–122.
- Williams, C.M., Ho Yuen, B., Klein, N.A. *et al.* (1998) Ovarian endometriomas during IVF treatment: do they affect outcomes? *Fertil. Steril.*, **70**, S19, 0–49.

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