

Article

Ethanol sclerotherapy: a treatment option for ovarian endometriomas before ovarian stimulation



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Abstract

Several surgical treatment modalities have been described in cases of isolated or multiple ovarian endometriotic cysts. The aim of this preliminary study was to investigate and test the efficacy of ethanol sclerotherapy (EST) for recurrent endometriotic cysts, before ovarian stimulation in infertile patients with an adequate ovarian status. In the setting of a prospective comparative study, EST was proposed to 31 infertile patients with recurrence of ovarian endometriomas before inclusion in assisted reproduction cycles. Reproductive outcome was compared with that of patients who had previous laparoscopic cystectomy for recurrent endometriomas. The mean size of endometriomas treated with sclerotherapy was 38.6 ± 11.2 mm in diameter. Ovarian cysts recurred in 12.9% of cases; at a mean time of 10 months after EST. Ovarian reserve and ovarian response to stimulation were better in the EST group than in the control group. Consequently, clinical and cumulative pregnancy rates of the study group were higher than those of the control group (48.3% versus 19.2%, $P = 0.04$; and 55.2% versus 26.9%, $P = 0.03$, respectively). Ethanol sclerotherapy may be a good alternative to surgical management of recurrent endometriotic cysts before assisted reproductive treatment. It could be advised for selected infertile patients.

Keywords: assisted reproductive technologies, ethanol, ovarian endometriotic cyst, ovarian reserve, sclerotherapy

Introduction

In recent years, various modalities of conservative surgery and treatment have been developed and conducted for ovarian endometriotic cysts. Conventional surgical treatment involved laparoscopic drainage of the cyst content with subsequent removal of the cyst wall (Canis *et al.*, 1995). In many cases, normal ovarian tissue is inadvertently removed (Muzii *et al.*, 2002), which may decrease ovarian reserve and the number of oocytes available for subsequent fertility treatment (Ragni *et al.*, 2005; Yazbeck *et al.*, 2006).

This is particularly true in patients, with advanced stage endometriosis, who have had multiple previous ovarian surgeries. In fact, patients and surgeons are uncomfortable with the idea of repeated surgery when pelvic adhesions are

generally expected. Avoiding such interventions is often a challenge before proceeding with assisted reproduction treatment.

Several reports studied the safety and efficacy of less invasive treatments of ovarian endometriomas. Simple ultrasound-guided aspiration of endometrial cysts was followed by invariable early recurrence (Vercellini *et al.*, 1992; Chan *et al.*, 2003). The efficacy of aspiration followed by sclerotherapy with 1% or 5% tetracycline has been reported (Aboulghar *et al.*, 1993; Chang *et al.*, 1997; Fisch and Sher, 2004). Japanese authors reported similar results using ethanol sclerotherapy (EST) for endometriomas (Okagaki *et al.*, 1999; Noma and Yoshida, 2001; Koike *et al.*, 2002).

EST has been used for various cystic lesions and is superior to simple aspiration according to the recurrence rate (Bean, 1981; Antonelli *et al.*, 1994).

The aim of this preliminary study was to investigate the efficacy of ethanol sclerotherapy for recurrent ovarian endometriomas before ovarian stimulation in infertile patients and to evaluate the reproductive outcome of these patients after such treatment.

Materials and methods

Population

Between November 2004 and February 2008, 35 infertile women with ultrasound evidence of post-surgical recurrence of ovarian endometriomas were offered sclerotherapy instead of repeated surgery in the setting of a prospective comparative study protocol. Inclusion criteria were: (i) positive histological diagnosis at previous surgery; (ii) recurrent endometriotic cysts; (iii) diameter between 2.0 and 6.0 cm; (iv) three or fewer cysts (unilateral or bilateral); (v) infertile patient in whom assisted reproductive technology was indicated; and (vi) acceptance of the treatment with a clear informed consent.

Ovarian reserve and reproductive outcome in the EST group was compared with those of a control group of 26 infertile patients, enrolled in the same period for assisted cycles, with a history of moderate-to-severe endometriosis including one conventional laparoscopic cystectomy for recurrent ovarian endometrioma. Treatment was undertaken in the same centre with similar ovarian stimulation protocols.

EST procedure for endometriotic cysts

EST was performed on an outpatient basis. After conscious oral sedation, the patient was placed in the lithotomic position. The vagina was carefully sterilized with povidone iodine. Under local anaesthesia and transvaginal ultrasound guidance, an 18-gauge 30 cm single lumen needle was inserted through the vaginal fornix into the endometrioma. The cyst content was aspirated and flushed with a volume of normal saline equal to double that of the aspirated volume. The aspirate was sent for pathological review. Pure sterile ethanol in an amount equal to 80% of the aspirated volume was then instilled into the cyst. If the calculated volume was more than 60 ml, the instilled ethanol value was determined to be 60 ml. Care was taken to avoid over distension, which could rupture the cyst and result in leakage into the pelvis. The procedure used was in accordance with that reported by Noma and Yoshida (2001). Ethanol was left in the cyst for a maximum of 10 min then aspirated as completely as possible. Volume loss, if any, was noted.

Tolerance of the procedure was evaluated by a visual analogue scale (VAS) rating the post-operative pain from 0 to 10 (Bodian *et al.*, 2001). An ultrasound evaluation was performed no less than 6 weeks later to assess the efficacy of treatment. If pregnancy occurred, follow-up was continued until after delivery. Recurrence was defined as the reappearance of a cyst of long diameter greater than 20 mm, the ultrasound features of which were consistent with ovarian endometriotic cysts.

Conventional treatment of infertility and assisted reproductive technology

Long acting gonadotrophin-releasing hormone agonist (Decapeptyl® 3 mg; Ipsen Biotech, France) was administered 2 weeks before EST in order to down-regulate the hypothalamic-pituitary axis. Ovarian stimulation was performed using the centre's standard protocols (Yazbeck *et al.*, 2006). All patients were eligible for stimulation 2 weeks after the procedure. An oestradiol, LH and progesterone control of axis suppression and an ultrasound verification of the absence of residual ovarian cysts were undergone at this time. Briefly, ovarian stimulation was performed using recombinant human FSH (Gonal-F® 900IU; Serono, France; or Puregon® 900IU; Organon, France) under daily subcutaneous Decapeptyl® 0.1 mg. Ovulation was triggered with recombinant human chorionic gonadotrophin (HCG; Ovitrelle®; Serono, France). Doses and regimens varied according to the ovarian status, stimulation history and patient's age and weight.

Oocytes were retrieved by transvaginal ultrasound guidance 36 h after HCG. Mature oocytes were fertilized using the study centre's standard IVF protocol. Intracytoplasmic sperm injection (ICSI) or intracytoplasmic morphologically selected sperm injection (IMSI) were used in couples with male factor and/or disorder of fertilization. Quality of embryos was assessed morphologically 3 days after fertilization and the best one to three embryos were transferred to the uterus using a soft catheter and ultrasound guidance. Ongoing pregnancy was defined as fetal heart activity and adequate growth at 12 weeks of gestation.

Statistical analysis

Statistical analysis was performed with SAS® v9.1 (SAS Institute Inc., USA). Data were reported as mean \pm SD or percentages. Mann-Whitney-Wilcoxon test for two-sample data, chi-squared and Fisher's exact tests were used as appropriate. The degree of significance (*P*-value) was set at <0.05 . Potential risk factors for recurrence were included in a logistic regression model with 90% confidence interval for estimates.

The study protocol was accepted by the French Institutional Committee of Protection of Patients undergoing Medical Research (CCPPRB) under the number 0611337 (Paris).

Results

EST was performed successfully in the study group ($n = 31$). Patient's age ranged between 24 and 40 years. The mean diameter of the largest endometriotic cyst was 38.6 ± 11.2 mm (Table 1). Eight patients (25.8%) had multiple cysts, which were bilateral in four cases (12.9%).

All cysts had macroscopic 'chocolate' content at aspiration. The mean volume of fluid aspirated was 22.1 ± 14.5 ml. The mean volume of ethanol injected was 17.3 ± 10.3 ml. Endometriosis was previously confirmed by histological analysis and no malignant cells were isolated from the aspirated fluid in any patient. No major complications during or after the procedure

(intraperitoneal haemorrhage, peritonitis, ovarian abscess, intestinal perforation or systemic acute alcoholism) were encountered. The procedure was well tolerated by more than 80% of the cases (mean VAS: 2.7 ± 1.9). Only one patient had an acute abdominal pain during sclerotherapy that resolved quickly after ethanol aspiration and was due to a loss of 1 ml of volume with probable cyst wall leakage.

All patients had subsequently undergone ovarian stimulation for assisted reproductive technology. Two patients had residual simple cysts at ultrasound control before ovarian stimulation and required a repeated aspiration with complete resolution. There was no sign of endometrioma recurrence in any patient at egg retrieval. However, the ovarian cysts recurred in 12.9% ($n = 4$) of cases (75% of these were non-pregnant and 25% were pregnant), at a mean time of 10 months after EST. The follow-up period ranged from 1.5 to 26 months. A logistic regression analysis showed that recurrence rate was not related to the patient's age, the size of the cysts, their number or the instillation time.

Table 2 illustrates the general characteristics of patients treated with EST and controls treated surgically. No significant differences were found with age, type and duration of infertility

between groups. However, higher basal FSH and oestradiol concentrations, and lower AMH concentrations were observed in the control group.

Ovarian stimulation and reproductive outcome are shown in **Table 3**. Eighty-seven per cent of patients in the EST group had a modified 'ultra-long' stimulation protocol with 3 mg of triptorelin, whereas 50% of the controls had a conventional 0.1 mg long protocol ($P < 10^{-4}$). The mean number of FSH units used and the technique were similar between groups. However, the number of oocytes retrieved and inseminated in the EST group (11.4 ± 6.1) was significantly higher than that in the control group (7.0 ± 4.7), $P = 0.03$. No differences were observed in the fertilization rate, the number of transferred embryos or the implantation rate.

After the first stimulation cycle, assisted reproductive technology treatment led to an ongoing gestation in 14 (48.3%; 95% CI 30.1–66.5%) of 29 IVF/ICSI cycles with embryo transfer. The control group had a significant lower ongoing pregnancy rate (19.2%; 95% CI 4.1–34.4%), $P = 0.04$. The cumulative pregnancy rate (after three cycles) was estimated at 55.2% (95% CI 37.1–73.3%) in EST group and 26.9% (95% CI 9.9–44.0%) in controls, $P = 0.03$.

Table 1. Ethanol sclerotherapy procedure details in patients with recurrent endometriomas ($n = 31$).

Parameter	Mean	SD	5th–95th percentiles
Diameter of the largest cyst (mm)	38.6	11.2	20.0–58.0
Volume aspirated (ml)	22.1	14.5	5.0–60.0
Volume of ethanol instilled (ml)	17.3	10.3	5.0–40.0
Duration of sclerotherapy (min)	8.1	2.5	5.0–11.0
Pain evaluation with VAS post procedure	2.7	1.9	1.0–7.0
Follow-up (months)	10.2	6.4	1.5–26.0

VAS = visual analogue scale.

Table 2. General characteristics in ethanol sclerotherapy and control groups.

	Treatment group ($n = 31$)	Control group ($n = 26$)	P-value
Age (years)	32.2 (4.0) [26.0–39.0]	31.8 (3.3) [28.0–38.0]	NS
Primary infertility, n (%)	24 (77.4)	19 (73.1)	NS
Duration of infertility (years)	5.3 (2.9) [2.0–12.0]	4.2 (3.1) [1.0–10.0]	NS
Ovarian reserve on day 3			
FSH (IU/l)	6.0 (1.5) [4.0–8.1]	9.0 (4.8) [2.6–14.0]	0.01
Oestradiol (pg/ml)	34.0 (13.8) [18.0–52.0]	46.7 (12.0) [28.0–77.0]	0.001
Inhibin B (ng/ml)	48.6 (21.6) [10.9–80.5]	50.9 (30.0) [15.0–122.0]	NS
AMH (ng/ml)	3.1 (2.0) [0.4–5.9]	2.2 (2.9) [0.04–13.5]	0.03
Antral follicle count ^a	9.6 (4.7) [5.0–22.0]	10.6 (6.8) [5.0–25.0]	NS

Values are mean (SD) [5th–95th percentile] unless otherwise stated.

AMH = anti-Müllerian hormone; EST = ethanol sclerotherapy; NS = not statistically significant.

^a50% of values missing.

Table 3. Ovarian stimulation and reproductive outcome of patients in ethanol sclerotherapy (EST) and control groups.

	EST group (n = 31)	Control group (n = 26)	P-value
Stimulation protocol, n (%)			<0.001 ^a
'Ultra-long' (3 mg triptorelin)	27 (87.1)	1 (3.8)	
Long (0.1 mg triptorelin)	3 (9.7)	13 (50.0)	
Short (0.1 mg triptorelin)	0 (0.0)	2 (12.5)	
Not specified	1 (3.2)	10 (38.5)	
Assisted reproduction technique, n (%)			NS
IVF	16 (51.6)	18 (69.2)	
ICSI	12 (38.7)	3 (11.5)	
IMSI	3 (9.7)	5 (19.2)	
Number of FSH 75 IU doses used ^b	32.6 (7.5) [21.0–47.0]	34.1 (17.7) [13.0–78.0]	NS
Oestradiol peak (pg/ml)	2311.8 (1294.3) [883.0–4822.0]	1698.5 (814.7) [536.0–2880.0]	NS
Total number of oocytes retrieved	11.4 (6.1) [2.0–21.0]	7.0 (4.7) [0.0–21.0]	0.03
Number of mature oocytes	10.4 (5.4) [2.0–21.0]	6.1 (3.8) [0.0–14.0]	0.02
Normal embryos at day 2	6.1 (3.1) [0.0–13.0]	4.5 (2.8) [0.0–11.0]	NS
Number of transferred embryos	2.1 (1.1) [0.0–4.0]	1.8 (0.6) [0.0–3.0]	NS
Fertilization rate (%)	60.8 (26.9) [0.0–100.0]	80.1 (25.5) [20.0–100.0]	NS
Implantation rate (%)	31.5 (38.4) [0.0–100.0]	32.3 (43.1) [0.0–100.0]	NS
Ongoing pregnancy rate	14 (48.3) [30.1–66.5]	5 (19.2) [4.1–34.4]	0.04
Cumulative pregnancy rate ^d	16 (55.2) [37.1–73.3]	7 (26.9) [9.9–44.0]	0.03

Continuous variables are represented by mean (SD) [5th–95th percentile]; categorical variables are represented by number (percentage) [95% confidence interval].

^aSignificant difference between long and 'ultra-long' protocols.

ICSI = intracytoplasmic sperm injection; IMSI = intracytoplasmic morphologically selected sperm injection.

Discussion

For women undergoing assisted reproduction treatment, there is a substantial controversy with respect to the most appropriate type of intervention for ovarian endometriomas (Donnez *et al.*, 1994). Even if removal of endometriomas before IVF–embryo transfer does not necessarily improve fertility outcomes (Garcia-Velasco *et al.*, 2004), cystectomy was generally indicated because non-operated large endometriomas may lead to difficulties in oocyte retrieval and to risks of ovarian abscess if inadvertently punctured. Furthermore, randomized prospective studies have focused on the benefit of cystectomy in decreasing recurrence rates and on improving clinical symptoms and spontaneous cumulative pregnancy rates (Beretta *et al.*, 1998; Alborzi *et al.*, 2004; Hart *et al.*, 2005). However, some authors have emphasized the deleterious effect of endometrioma excision on residual ovarian cortex before IVF (Ho *et al.*, 2002; Somigliana *et al.*, 2003; Ragni *et al.*, 2005; Yazbeck *et al.*, 2006).

The present study suggests that EST may be a good alternative to surgery particularly in recurrent ovarian endometriotic cysts. After ethanol sclerotherapy of endometriotic cysts, the recurrence rate (12.9%) was similar to that reported, 13.3% (Koike *et al.*, 2002), and lower than that reported with 5% tetracycline, 46.9% (Chang *et al.*, 1997) and 25.0% (Fisch and Sher, 2004). According to Noma and Yoshida (2001), this low recurrence rate may be related to the time of ethanol instillation, which was about 8 min in this study.

EST does not appear to adversely affect reproductive outcome in these infertile women undergoing assisted reproductive technology. The ongoing and cumulative pregnancy rates in the study group were higher than those after the conventional surgical management of recurrent endometriotic cysts. These results are consistent with those from previous studies (Chang *et al.* 1997; Fisch and Sher, 2004).

A reduced ovarian reserve was observed in the control group and could explain the lower pregnancy rate in these patients. This observation may be due to the deleterious effect on ovarian tissue and vascularization from repeated surgery. The higher pregnancy rate after sclerotherapy could also be explained by a more frequent use of the modified 'ultra-long' gonadotrophin-releasing hormone agonist protocol in this group. Prolonged pituitary suppression prior to IVF or ICSI in women with endometriosis has proved to increase the odds of clinical pregnancy by four-fold (Sallam *et al.*, 2006). Suppression in these cases varied between 3 and 6 months, whereas it was limited to 30 days in this study group. Potential effects of prolonged suppression might not be as important in this population since the difference with the standard protocol was only 15 days.

Many clinicians are daunted by the risk of pelvic abscess following insertion of a needle into an ovarian endometrioma (Younis *et al.*, 1997) or the risk of missing an early occult malignancy. While no such complications were encountered in this study, rigorous sterile technique should be used invariably

to minimize the risk of secondary infection. The risk of encountering a malignancy is small, estimated at 0.7% (Nishida *et al.*, 2000), especially in this young population. However, careful selection of patients, based on history and ultrasound diagnosis, and pathological evaluation of aspirated cyst fluid could further reduce this risk. Eventually, in cases where there is still a doubt as to the aetiology, surgical evaluation remains the method of choice.

In conclusion, ethanol sclerotherapy may be relevant for infertile patients with recurrent endometriotic cysts, but is not intended to replace laparoscopy in the treatment of ovarian endometriosis. EST helps to preserve follicular ovarian reserve in a population already at risk for decreased ovarian reserve, especially in the case of repeated surgery. In this preliminary study, EST of endometriomas was found to be well tolerated and effective. However, due to the limited possibility of adhesion formation, EST treatment is proposed mainly for patients planning to undergo IVF, and not for those trying to conceive on their own. Detailed patient counselling is mandatory. Patients must be aware of the advantages, the limitations and the risks of this kind of procedure.

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