Conservative Management versus Aspiration of Functional Ovarian Cysts Before Ovarian Stimulation for Assisted Reproduction

GABRIEL E. FISZBAJN,^{1,2} RUBÉN G. LIPOWICZ,¹ LAURA ELBERGER,¹ ADRIANA GRABIA,¹ SERGIO D. PAPIER,¹ SANTIAGO P. BRUGO OLMEDO,¹ and CLAUDIO F. CHILLIK¹

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Purpose: To compare the efficiency of transvaginal ultrasound-guided functional ovarian cyst aspiration, with conservative management, in the outcome of patients undergoing assisted reproductive technique (ART) (in vitro fertilization or intracytoplasmic sperm injection). These cysts were identified before ovarian stimulation begun and after administration of a midluteal GnRH agonist.

Methods: Fifty nine patients undergoing ART from January 1, 1997 to February 28, 1999, who developed functional ovarian cysts were included. Aspirations of these cysts (n = 14) versus conservative management (observation) (n = 45) were compared. Total number of ovarian follicles developed, number of oocytes retrieved, estradiol levels on the day of human chorionic gonadotropin, fertilization rate, number of good quality embryos transferred, implantation, and clinical pregnancy rate per cycle were evaluated.

Results: No statistical differences were observed between the two groups in any of the selected parameters.

Conclusions: Cyst aspiration and conservative management showed similar implantation and pregnancy rates, in patients who develop functional ovarian cysts after pituitary down-regulation following luteal phase gonadotropin-releasing hormone agonist administration. Prospective studies are needed to confirm this trend.

KEY WORDS: assisted reproductive technique; transvaginal aspiration; functional ovarian cysts; GnRH agonists; ovarian stimulation.

INTRODUCTION

The use of gonadotropin-releasing hormone (GnRH) analogue (GnRH-a) to induce ovarian suppression was

first reported in 1984 by Porter *et al.* (1). Since then, GnRH-a has been widely used preceding the stimulation with gonadotropins for in vitro fertilization–embryo transfer (IVF-ET) programs. In 1987, Waegemaekers *et al.* (2) were the first to describe the formation of functional ovarian cysts with the use of GnRH-a. According to previous reports, these cysts appear in a high percentage of cases (3–6) and are a result of the initial stimulatory or flare-up effect of the GnRH-a.

Patients with functional ovarian cysts represent a decision challenge for proper management. Some authors recommend aspiration of the cysts (2,7,8); others continue with the analogue administration, maintaining a conservative management (observation) until ovarian suppression is achieved (4,9).

The purpose of this retrospective study was to compare both treatment modalities in terms of results of assisted reproductive technique (ART) performance in these patients.

MATERIALS AND METHODS

We evaluated 59 cycles from patients undergoing an assisted reproductive procedure [IVF or intracytoplasmic sperm injection (ICSI)] at the Centro de Estudios en Ginecología y Reproducción (CEGyR) between January 1, 1997 and February 28, 1999, that presented with functional ovarian cysts during administration of luteal phase GnRH-a. We defined a functional cyst as a round, well-limited, anechoic structure, with a diameter >15 mm in the ultrasound at the time of the postsuppression control, accompanied by serum estradiol (E₂) level $\geq$ 50 pg/ml.

All patients had normal basal ultrasound examination or normal basal E₂ profile (day 3), performed the

¹ Centro de Estudios en Ginecología y Reproducción, Viamonte 1438 (1055), Buenos Aires, Argentina. (Affiliated with the University of Buenos Aires, School of Medicine).

² To whom correspondence should be addressed.

month before the beginning of the treatment. Therefore, the presence of previous functional cysts could be ruled out.

Patients who received GnRH-a (Lupron 2.8 ml; Abbott, Argentina) in a luteal-phase suppressor protocol, using daily subcutaneous doses of 1 mg or 0.5 mg, were included. Ovarian suppression was confirmed with vaginal ultrasound, demonstrating absence of ovarian function and a resting endometrium with an E_2 level ≤ 50 pg/ml. Controlled ovarian hyperstimulation was performed with 300 IU of recombinant, high purified, or pure follicle-stimulating hormone (FSH) (Gonal-F, Metrodine HP, Serono, Argentina; Follitrin, Massone, Argentina), or with a combination of 150 IU of FSH and 150 IU of human menopausal gonadotropin (hMG) (Pergonal 1000, Serono, Argentina; hMG Massone, Argentina) according to physician's criteria, and at that time, the analogue was decreased to 0.5 or 0.25 mg/day. Ovarian monitoring was started on day 5 of the stimulation with vaginal ultrasounds and serum E_2 determinations, and was repeated every 24–48 hr as required in each case. A dose of 10,000 IU of human chorionic gonadotropin (hCG) (Profasi HP, Serono, Argentina) was administered when at least two follicles >16 mm were visualized. Oocyte aspiration was performed 35 hr after hCG administration under vaginal ultrasound guidance. Fertilization was achieved through IVF or ICSI. Embryo transfer was performed using a Frydman cannula 48 hr after oocyte retrieval. A daily dose of 800 mg micronized progesterone was administered transvaginally (Utrogestan, Rontag, France), beginning on the day after oocyte retrieval and until the confirmation of pregnancy; progesterone was continued thereafter until the 12th week of gestation.

Ultrasonography was performed using an endovaginal 7.5 mHz transducer and an Aloka SSD-680 unit (Aloka Co. Ltd., Japan). Serum E_2 was determined by the COAT-A COUNT IRMA Kit (Diagnostic Products Corporation, Los Angeles, CA), a solid-phase immunoradiometric assay. Intrassay and intra-assay coefficient of variation were 5.9% and 4.9%, respectively.

All patients who developed cysts between the beginning of the treatment with GnRH-a and the start of controlled ovarian hyperstimulation (COH) were divided in two groups. Group A consisted of 45 patients (41 embryo transfers), in which conservative management was used. COH was begun when serum estradiol level was < 50 pg/ml. Group B included 14 patients (13 embryo transfers), in which the cyst was aspirated under ultrasound guidance. Before COH was

Table I. Clinical Features of the Patients in Groups A and B^a

	Group A (n = 45)	Group B (n = 14)	P values
Age (years)	32.91 $\pm$ 3.94	33.43 $\pm$ 4.33	0.68 (NS)
Basal FSH (IU/ml)	6.77 $\pm$ 3.63	4.94 $\pm$ 2.65	0.13 (NS)
Basal LH (IU/ml)	5.18 $\pm$ 2.13	3.61 $\pm$ 1.17	0.30 (NS)
Basal FSH/LH ratio	1.52 $\pm$ 0.89	1.54 $\pm$ 1.17	0.95 (NS)

^a All values are means $\pm$ SD. NS, Nonsignificant; $P < 0.05$ = significant (S).

started in this group, we confirmed ovarian suppression with a serum estradiol level < 50 pg/ml.

Statistical evaluation was performed using student's t and χ^2 tests. Statistical significance was defined as $P < 0.05$, and the results are expressed as mean $\pm$ SD.

RESULTS

An incidence of functional ovarian cysts of 5.5% (59 cases out of 936 procedures performed during the studied period) in GnRH-a treated patients was detected. Both groups were similar in terms of cause of infertility and dose of the analogue. There were no significant differences between groups A and B in terms of age, basal FSH and luteinizing hormone (LH) levels, and FSH:LH ratio (Table I). Serum E_2 levels post-GnRH-a suppression, E_2 on the day of hCG, number of oocytes retrieved, fertilization rate, number of embryos transferred, implantation rate, and clinical pregnancy rate per transfer (defined as transvaginal ultrasound visualization of a gestational sac at 6 weeks gestational age) were also similar, as shown in Table II.

In group A, 15 clinical pregnancies were obtained, 3 of which were twin pregnancies and 4 ended in clinical miscarriages (1 twin). In group B, 5 clinical pregnancies were diagnosed, 3 of which were twin pregnancies and 2 ended in clinical miscarriages (1 twin). Finally, the implantation and clinical pregnancy rates also were not statistically different, although a trend in favor of group B was observed.

DISCUSSION

One of the most frequent complications of the administration of GnRH-a is the formation of functional ovarian cysts, regardless of the protocol used (luteal or follicular long protocol or short flare-up protocol). The incidence of the formation of these cysts is quite variable. Jenkins *et al.* (7) reported an incidence

Table II. Results^a

	Group A (n = 45)	Group B (n = 14)	P values
E ₂ post GnRHa. (pg/ml)	229.24 ± 403.83	211.5 ± 137.16	0.88 (NS)
E ₂ after suppression (pg/ml)	25.06 ± 17.81	27.92 ± 30.95	0.70 (NS)
E ₂ (day of hCG) (pg/ml)	1148.74 ± 932.68	1080.64 ± 680.50	0.80 (NS)
Number of preovulatory oocytes	11.16 ± 8.50	11.46 ± 8.22	0.91 (NS)
Fertilization rate (%)	61.55 ± 27.66	55.71 ± 35.77	0.54 (NS)
Number of good quality embryos transferred	2.58 ± 1.14	2.43 ± 1.34	0.68 (NS)
Implantation rate (%)	13.79	23.53	0.44 (NS)
Clinical pregnancy rate per transfer (%)	24.44	35.71	0.30 (NS)

^a All values are means ± SD. NS, Nonsignificant; $P < 0.05$ = significant (S).

of 6%, while Meldrum *et al.* (10) and Feldberg *et al.* (3) found approximately 25%. These discrepancies between different reports could be due to different definitions of cyst, between 10 and 30 mm, as well as to different times of administration and dose of the analogue. An average incidence of 13.6% was reported by Herman *et al.* (4) in 1990. In our study, we detected 59 cases from the 936 procedures performed during the period studied, which represents an incidence of 5.5%.

Jenkins *et al.* (5) demonstrated in 1993 that these cysts are of follicular origin. It was suggested that the cysts are formed from immature antral follicles in response to the initial flare up generated by the GnRH-a. The subsequent desensitization of the hypophysis inhibits the LH surge, generating a disorder in follicular growth and formation of the cyst. The E₂ levels therefore can continue to be elevated from an active cyst production, despite the pituitary suppression achieved with the GnRHa.

There are different mechanisms through which these cysts can influence ART results. The first is a functional endocrine effect with disruption of early stages of the follicles. Another mechanism is by premature luteinization and elevation on the serum progesterone (lutein cyst). The third is mechanical through a reduction of space for follicle growth, or through impairment of the ovarian blood flow.

Rizk *et al.* (8) demonstrated that there are no significant differences in IVF results whether the cysts are aspirated or conservative management is used. However, they do not discriminate whether these cysts are functional or not, or the time during the cycle that the suppressor therapy was administered. We agree with their conclusion, because no significant differences were found in our material between both groups in terms of final results. It has been demonstrated that the failure to achieve an E₂ suppression level in the presence of functional ovarian cysts does not necessarily

imply a failure in the pituitary desensitization by the GnRH-a (11).

Keltz *et al.* (9) reported that the formation of these cysts is an indication of poor response, as well as a reliable predictor of poor stimulation and low pregnancy rates in IVF-ET cycles, but they did not establish a norm to handle these particular type of patients. Ron-El *et al.* (6) demonstrated that conservative management of these patients does not significantly affect either the number or the quality of the oocytes and embryos. However, in this study, the cysts were formed during the administration of the analogue, beginning in the follicular phase. But, as demonstrated in our study, even if the analogue administration is begun in the luteal phase, the quantity and quality of the embryos obtained (Table II) does not vary significantly in comparison with the patients who did not present functional ovarian cysts. Tarlatzis *et al.* (12) did not find significant differences regarding the number of follicles and oocytes in those patients who developed cysts that were punctured and in those who did not develop cysts. He suggests the convenience of puncturing the cysts more from a clinical impression than scientific criteria.

No other study in the literature reviewed compares the different ways of managing this specific type of functional cyst produced after the administration of GnRHa in the luteal phase. Therefore, our study intended to contribute new data to establish guidelines in the management of this specific situation.

CONCLUSIONS

According to our results, the aspiration of functional ovarian cysts under transvaginal ultrasound guidance, compared to an expected behavior, after obtaining ovarian suppression ($E_2 \leq 50$ pg/ml), and before begin-

ning ovarian stimulation, has similar results in regard to implantation and pregnancy rates. However, a tendency was observed in favor of the first management. In addition, the aspiration of these cysts has some beneficial effects, such as a decrease in the amount of the analogue used and a shorter period of the time needed to start ovarian stimulation.

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