Ovarian cyst formation following GnRH agonist administration in IVF cycles: incidence and impact

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BACKGROUND: The formation of functional ovarian cysts has been recognized as one of the side effects of GnRH agonist administration. The formation of cysts during IVF treatment may be of no clinical significance or may negatively influence its outcome. The objective of this study was to determine the incidence of ovarian cyst formation following GnRH agonist administration and to examine their effect on IVF outcome. METHODS: A prospective study of 1317 IVF patients who developed one or more functional ovarian cysts of \( \geq 15 \) mm following GnRH agonist treatment was performed. Transvaginal ultrasonographic-guided cyst aspiration was carried out in 76 randomly allocated patients out of 122 patients who were found to have functional ovarian cysts before starting ovarian stimulation with gonadotropins. RESULTS: The incidence of follicular cyst formation was 9.3%. Cyst cycles in comparison with non-cyst cycles had significantly elevated day 3 basal FSH (mean ± SD of 8.3 ± 3.2 versus 5.3 ± 2.6 mIU/ml, \( P < 0.05 \)) and required more ampoules of gonadotropins (46.3 ± 16.5 versus 35 ± 14.6, \( P < 0.01 \)). Furthermore, they showed a statistically significant decrease in the quality and number of oocytes retrieved, fertilization rate, number and quality of embryos, implantation and pregnancy rates, with a significant increase in cancellation and abortion rates. Patients with bilateral cysts had a significantly lower number of oocytes and embryos retrieved, with a lower proportion of metaphase II oocytes. They also had a higher proportion of poor quality embryos. Cyst aspiration was not associated with a significant difference in the above parameters. CONCLUSIONS: The incidence of cyst formation during GnRH agonist treatment is lower than previously reported. In such cases, the quality of oocytes and embryos were significantly compromised, with a significant increase in the cycle cancellation rate and a decrease in the implantation and pregnancy rates. Neither conservative management nor cyst aspiration improved the IVF outcome.

Key words: follicular ovarian cyst/GnRH agonist/in vitro fertilization/pregnancy rate

Background

One known complication of pituitary down-regulation using GnRH agonist in IVF treatment cycles is the formation of functional ovarian cysts (Feldburg et al., 1989; Rizk et al., 1990; Jenkins et al., 1992, 1993; Parinaud et al., 1992; Tarlatzis et al., 1994; Keltz et al., 1995; Segal et al., 1999; Biljan et al., 2000). The incidence of these cysts is reported to range between 8% and 53% (Feldburg et al., 1989; Parinaud et al., 1992; Keltz et al., 1995; Biljan et al., 2000).

Functional ovarian cyst formation had been reported following various IVF protocols (short and follicular or luteal long GnRH agonist protocols) (Rizk et al., 1990; Tarlatzis et al., 1994; Keltz et al., 1995), different types of GnRH agonist (short and long acting forms), the concomitant use of HMG (Parinaud et al., 1992) and in older women with decreased ovarian reserve (Keltz et al., 1995).

The precise mechanism by which these cysts are formed is unknown. Possible explanations include the initial transient flare up effect of the GnRH agonist on gonadotropins (Feldburg et al., 1989), insufficient suppression of the circulating gonadotropins to hypophysectomy levels (Jenkins et al., 1992), the direct effect of GnRH agonist on the ovaries and steroidogenesis (Parinaud et al., 1992), and the serum progesterone level at the time of GnRH agonist administration (Jenkins et al., 1993).

It has been suggested that the formation of cysts during IVF treatment is of no clinical significance (Jenkins et al., 1992; Keltz et al., 1995; Segal et al., 1999) or to negatively influence its outcome (Feldburg et al., 1989; Parinaud et al., 1992; Tarlatzis et al., 1994; Biljan et al., 2000). We conducted this study to determine the incidence of functional ovarian cyst formation following GnRH agonist administration and to examine their effect on the outcome of IVF treatment.

Patients and methods

Between January 2002 and December 2003, a total of 1317 infertile women underwent a single IVF treatment cycle using a standardized pituitary down-regulation protocol, namely long-luteal pituitary...
down-regulation using the GnRH analogue triptorelin (Decapeptyl: Ipsen, Paris; France), which commenced on day 21 of the menstrual cycle. Patients with non-functional ovarian cysts were excluded.

A transvaginal ultrasound scan was performed and a blood sample was taken to measure estradiol (E2) levels on the third day of bleeding following GnRH agonist administration. A functional ovarian cyst was defined as a thin-walled intraovarian sonolucent structure with a mean diameter of ≥15 mm and E2 levels of ≥50 pg/ml.

Women who developed ovarian cysts were randomly divided into two groups: (i) group I underwent cyst aspiration (n = 76); and (ii) group II (n = 46) had no intervention. An algorithm of patients flow and allocation scheme for the study is summarized in Figure 1. Randomization was accomplished using a selection from a table of random numbers available in a standard statistics textbook.

Cyst aspiration under local anaesthesia was performed on the day of diagnosis. Ovarian stimulation with HMG was started in all patients on the third day of bleeding. Transvaginal ultrasound follow-up for follicular growth was commenced on day 8 of ovarian stimulation and repeated every 3–4 days thereafter. When at least three follicles reached a mean diameter of 17 mm, a single dose of 10,000 IU HCG was administered. After 36 hours, transvaginal-guided oocyte retrieval was performed under general anaesthesia.

Fertilization was considered successful after noting the presence of two pronuclei and second polar body 20–24 h after conventional IVF by adding ~10^5 motile spermatozoa/ml to droplets of medium each containing one oocyte or after ICSI.

Embryos were graded as previously described by Coskun et al. (1998). Good embryos included those with even-sized blastomeres and no obvious fragmentation or even-sized with <10% fragmentation or uneven-sized with no obvious or <10% fragmentation. Fair embryos included those with 10–30% fragmentation. Embryos with >30% fragmentations were considered poor.

Embryos were transferred 72 h following oocyte retrieval using a Wallace catheter (Marlow Surgical Technology, Willoughby, OH, USA). Progesterone pessaries (Cyclogest: Alpharma, Barnstaple, Devon, UK) were used for luteal phase support. Two weeks after embryo transfer, serum β-HCG was requested and pregnant women had an ultrasound scanning at 6 weeks gestation. Demonstration of intrauterine fetal pole with positive fetal heartbeat was defined as clinical pregnancy. The possibility of having a lower chance of pregnancy was explained to all patients with ovarian cysts who enrolled late and an informed consent was obtained. The department of obstetrics and gynaecology review board was informed of the findings.

Statistical analysis was presented as mean ± SD and percentages. Chi-Square test and Student-t test were used as appropriate. A P value of ≤0.05 was considered statistically significant.

**Results**

The demographic data of women with and without ovarian cyst formation after GnRH agonist administration are presented in Table I. A total of 1317 infertile women were recruited for IVF treatment. Their ages ranged between 21–43 years (mean ± SD: 31 ± 4.2 years). Duration of infertility ranged between 2–19 years (mean ± SD: 6 ± 4.2 years). Causes of infertility included anovulation, endometriosis, unexplained infertility, tubal and male factor. Of the 1317 women, 1195 had no evidence of ovarian cyst while the remaining 122 patients developed ovarian cysts (an incidence of 9.3%). The age and duration of infertility in patients with ovarian cysts did not differ significantly from those without cysts. There were no significant differences in the aetiology of infertility between the two groups.

![Figure 1](image-url)  
*Figure 1. Algorithm of patient flow and allocation scheme for the study.*
The cycle characteristics and outcome of women who developed unilateral and bilateral ovarian cysts are presented in Table III. Patients with bilateral ovarian cysts (25.4%) had a significantly higher E₂ level and a higher proportion of poor quality embryos (P < 0.05) than those in the unilateral group. Furthermore, the number of follicles ≥14 mm, number of oocytes retrieved and number of day 2 embryos were significantly lower compared with the unilateral cyst group. There were no significant differences between the two groups in terms of cancellation rate, number of embryos transferred, fertilization, pregnancy and abortion rates.

Of the 122 women with ovarian cysts, 76 (62.3%) underwent ovarian cyst aspiration. There were no significant differences in the average size of the cysts or the E₂ levels on the day of diagnosis between the aspirated and the non-aspirated group. The ‘cyst aspiration’ group showed a significant difference in the number of HMG stimulation days or in the number of ampoules required compared with the ‘no-aspiration’ group. There were no significant differences in terms of cancellation rate, number of oocytes retrieved, fertilization rate, quality of embryos, number of embryos transferred, pregnancy and abortion rates (Table IV).

Discussion

To our knowledge, this is the largest study conducted to examine the incidence of functional ovarian cyst formation following GnRH agonist administration and the effect of these cysts on the outcome of conventional IVF and ICSI treatment. Furthermore, this is the first study that examines the outcome of IVF treatment in relation to unilateral and bilateral cyst formation.

In our study, the incidence of ovarian cyst formation following GnRH agonist treatment was 9.3%. Using the same criteria of functional ovarian cysts of ≥15 mm and E₂ levels of ≥50 pg/ml, other investigators had reported a higher incidence—33.3% as reported by Keltz et al. (1995), 14.5% by Tarlatzis et al.
Table IV. Cycle characteristics and outcome of IVF patients who underwent functional ovarian cyst aspiration and those who did not

<table>
<thead>
<tr>
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<th>Cyst aspiration group (n = 76)</th>
<th>No-cyst aspiration group (n = 46)</th>
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<tbody>
<tr>
<td>Cyst diameter (mm)</td>
<td>22 ± 6</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>E2 levels on day of diagnosis (pg/ml)</td>
<td>178 ± 26.8</td>
<td>183.5 ± 25.9</td>
</tr>
<tr>
<td>Days of stimulation with HMG</td>
<td>14.4 ± 3.3</td>
<td>16.4 ± 4.3</td>
</tr>
<tr>
<td>No. of ampoules of HMG</td>
<td>42.2 ± 12.7</td>
<td>45.3 ± 19.4</td>
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<tr>
<td>No. of follicles &gt; 14 mm</td>
<td>5.4 ± 3.1</td>
<td>5 ± 2.9</td>
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<tr>
<td>No. of oocytes retrieved</td>
<td>5.6 ± 1.8</td>
<td>5.2 ± 2.1</td>
</tr>
<tr>
<td>Metaphase II oocytes (%)</td>
<td>(32)</td>
<td>(29)</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>(50.9)</td>
<td>(44.7)</td>
</tr>
<tr>
<td>Pregnancy rate (%) 6/59</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Pregnancy rate %</td>
<td>(25.5)</td>
<td>(13.9)</td>
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<tr>
<td>Grades of embryos</td>
<td></td>
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<tr>
<td>Good (%)</td>
<td>(15.9)</td>
<td>(16.9)</td>
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<tr>
<td>Fair (%)</td>
<td>(25.5)</td>
<td>(13.9)</td>
</tr>
<tr>
<td>Poor (%)</td>
<td>(58.6)</td>
<td>(69.2)</td>
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<tr>
<td>No. of embryos transferred</td>
<td>2.1 ± 1.4</td>
<td>2.1 ± 1.2</td>
</tr>
<tr>
<td>Cancellation rate (%)</td>
<td>18/76 (23.7)</td>
<td>11/46 (23.9)</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>(4.3)</td>
<td>(4.1)</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>6/59 (10.2)</td>
<td>3/34 (8.8)</td>
</tr>
<tr>
<td>Abortion rate (%)</td>
<td>2/6 (33.3)</td>
<td>1/3 (33.3)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. Values in parentheses are percentages.

The activation of the endocrine–paracrine pathway has been suggested as another mechanism by which functional ovarian cysts may affect IVF results (Penzias et al., 1994; Ghosh and Sengupta, 1998). In a similar study to this one but with smaller sample size, Keltz et al. (1995) noted cyst formation in 26 out of 78 cycles (33.3%). In their series, patients with ovarian cysts compared with the no-ovarian cysts group had significantly higher cancellation rate and showed significant decrease in the number of retrieved oocytes, total number of embryos, fertilization and pregnancy rates. ‘Cyst cycles’ were associated with significantly higher basal levels of FSH.

A negative impact of ovarian cysts on folliculogenesis was recently reported by Segal et al. (1999). A higher incidence of ovarian cyst formation was reported in their series (51.8%), but their cyst diameter criterion was ≥10 mm. The pregnancy rate in the ‘cyst cycles’ was 24% versus 41% in the ‘non-cyst cycles’. In our study, the pregnancy rate was 9.7% versus 29.7%. This discrepancy is possibly because our patients were at a higher risk of being poor responders as manifested by their significantly elevated basal FSH levels. This study was disadvantaged by the smaller sample size of 137 patients compared with 1317 in our study.

In contrast, other studies have reported no detrimental effect due to functional cyst formation following GnRH agonist treatment (Feldburg et al., 1989; Ron-El et al., 1989; Herman et al., 1990; Parinaud et al., 1992; Tarlatzis et al., 1994; Biljan et al., 2000; Owj et al., 2004). Furthermore, they have demonstrated no difference in the incidence of cyst formation in different GnRH agonist type groups. Tarlatzis et al. (1994) studied 141 women using three different types of GnRH agonist in the long protocol and reported an overall functional cyst formation incidence of 14.5%; they concluded that the presence of such cysts did not interfere with induction of ovulation or achievement of pregnancy. In a recent study, Biljan et al. (2000) observed cyst formation in 27 out of 51 (52.9%) cycles. Similar to the findings of our study, in their series patients who developed ovarian cysts required a significantly longer time to achieve pituitary suppression and higher doses of gonadotropins. In contrast, the implantation and pregnancy rates were significantly lower in our study, whilst Biljan et al. (2000) reported no difference in the pregnancy rates between the cyst and non-cyst groups. This discrepancy may be related to the smaller size of their study.

In a more recent study by Owj et al. (2004), unexpected results were found when comparing 39 women who developed ovarian cysts with 42 who did not. Owj et al. (2004) found that the number of oocytes, MII oocytes retrieved and embryos was significantly higher in the ovarian-cyst group compared with controls. Their study lacked a possible explanation of the mechanism.

In order to improve folliculogenesis and IVF outcome, different approaches have been described for the management of women with follicular ovarian cyst development following GnRH agonist administration. These include conservative management with prolonged down-regulation (Feldburg et al., 1989; Thatcher et al., 1989; Ron-El et al., 1989; Keltz et al., 1995; Segal et al., 1999; Biljan et al., 2000; Owj et al., 2004) and progesterone therapy during pituitary desensitization (Engmann et al., 1999).
Aspiration of functional ovarian cysts has been advanced as an alternative to improve IVF outcome. Consistent with our findings, no significant difference was demonstrated in the number of retrieved oocytes, embryo quality, fertilization rate, implantation and pregnancy rates between women whose cysts were aspirated and those whose cysts were not (Rizk et al., 1990; Parinaud et al., 1992; Tarlatzis et al., 1994).

In summary, the current study demonstrates that the incidence of ovarian cyst formation following GnRH agonist administration before controlled ovarian hyperstimulation for the purposes of IVF treatment is 9.3%. This may reflect the true incidence before controlled ovarian hyperstimulation for the purposes of ovarian cyst formation following GnRH agonist administration. Such cysts were present bilaterally as opposed to being present unilaterally, the number and quality of oocytes and embryos, and the implantation and pregnancy rates were negatively affected to a statistically significant degree as compared with ‘non-cyst’ cycles. Furthermore, when such cysts were present bilaterally as opposed to being present unilaterally, the number and quality of oocytes and embryos were further compromised, but without a significant affect on the implantation and pregnancy rates. Cysts aspiration before ovarian stimulation was of no added benefit.

References


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