Empty follicle syndrome: evidence for recurrence

T.G.Zreik, J.A.Garcia-Velasco¹, T.M.Vergara, A.Arici, D.Olive and E.E.Jones

Yale University School of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, 333 Cedar Street, New Haven, CT 06520, USA

¹To whom correspondence should be addressed: IVI-Madrid, C/Santiago de Compostela 88, 28035 Madrid, Spain

The empty follicle syndrome (EFS) is a frustrating condition in which no oocytes are retrieved in an IVF cycle. Although this is an infrequent event in IVF patients, the economic consequences as well as the emotional frustration of a cancelled cycle due to the inability to obtain oocytes are enormous. The mechanisms responsible for EFS remain obscure, though many hypotheses have been put forward ranging from dysfunctional folliculogenesis to a drug-related problem. We found that the EFS is a rare event (1.8% of oocyte retrievals) but with profound implications for counselling the couple about their future reproductive performance. The chances of recurrence of EFS increase with the age of the patient (24% recurrence rate for the 35–39 year age group, and 57% for those over 40 years). We postulate that ovarian ageing, through altered folliculogenesis, may be implicated in the aetiology of EFS and its recurrence.

Key words: empty follicle syndrome/failed oocyte retrieval/human chorionic gonadotrophin/IVF/recurrence

Introduction

It has been more than a decade since the concept of empty follicle syndrome (EFS), in which no oocytes are retrieved in an IVF cycle, was introduced (Coulam et al., 1986). EFS has been reported to occur in natural as well as stimulated cycles in which multiple follicles develop yet no oocytes are retrieved. The incidence of this syndrome in patients undergoing IVF has been estimated to be about 2–7% (Ben-Shlomo et al., 1991), although a more recent report suggests a lower incidence (Awonuga et al., 1998).

The underlying mechanism of EFS remains hypothetical. It was suggested that this is not a syndrome but rather a sporadic event that cannot be predicted by the pattern of ovarian response either sonographically or hormonally (Ben-Shlomo et al., 1991). An alternative suggestion was that it might reflect dysfunctional folliculogenesis, with early oocyte atresia and apparently normal hormonal response (Tsuiki et al., 1988). For others (Zegers-Hochschild et al., 1995; Ndukwe et al., 1996), the EFS is interpreted solely as a drug-related syndrome, resulting from an abnormality in the biological activity of some batches of human chorionic gonadotrophin (HCG). However, this approach fails to explain the recurrence of the syndrome (Coulam et al., 1986; La Sala et al., 1991; Khalaf and Braude, 1997).

Furthermore, the significance of the failure to retrieve oocytes during one IVF cycle to the future fertility of the patient or to the risk of recurrence of EFS in future IVF cycles remains speculative. We therefore undertook this study to evaluate the risk of recurrence of this syndrome in IVF cycles.

Materials and methods

All cases of failed oocyte recovery in IVF cycles from 3004 oocyte retrievals performed between January 1987 and December 1996 at Yale IVF Centre were identified through a retrospective chart review. A total of 37 patients who underwent a total of 202 IVF cycles, either natural or stimulated, and who had at least one EFS cycle were evaluated. Two patients who underwent a total of only one IVF cycle each were excluded from further analysis. The remaining 35 patients who underwent more than one IVF cycle were divided into two groups, those having a single EFS cycle (n = 27; group I) and those who had more than one EFS cycle or recurring empty follicle cycles (n = 8; group II).

Patients underwent a complete infertility evaluation including basal body temperature recordings, midluteal endometrial biopsies, and/or serum progesterone concentrations, hysterosalpingography, postcoital testing, and semen analyses of the male partner. Unexplained infertility was defined by normal findings in the above-mentioned infertility evaluation and included normal laparoscopic findings or minimal endometriosis. Direct laparoscopic visualization with or without biopsy of suspicious lesions was used to confirm endometriosis.

A standard IVF protocol was used. Briefly, gonadotrophin releasing hormone agonist (leuprolide acetate; TAP Pharmaceuticals, Deerfield, IL, USA) was administered 0.1 mg/day s.c., starting in the midluteal phase of the preceding cycle or the first day of stimulation cycle. Stimulation with gonadotrophins [human menopausal gonadotrophin (HMG), urofollitrophin (uFSH), or uFSH high purity] (Pergonal/Metrodin/Metrodin HP; Serono Laboratories, Norwell, MA, USA) was initiated when there was no sonographic evidence of ovarian follicular activity and serum oestradiol concentration was <50 pg/ml (conversion factor to SI unit, 3.671), and was continued until oestradiol concentrations reached ≥500 pg/ml and at least two follicles ≥18 mm diameter were present. At that time 10 IU HCG (Profasi; Serono Laboratories) was administered and leuprolide acetate and HMG were discontinued. Oocyte retrieval by transvaginal ultrasound guidance was performed at ~34 h after HCG administration. Oocyte maturity was graded by the morphological appearance of the oocyte–cumulus complex (OCC). Oocytes and spermatocytes were incubated at 37°C in 5% CO2 and air. Embryos were graded (I, good to V, poor) on the day of transfer according to their morphology under the inverted microscope and transferred transcervically into the uterus. Pregnancies
were diagnosed by a rising concentration of serum β-HCG test, which was performed 14 days after embryo transfer. Clinical pregnancies were determined by the presence of a gestational sac on transvaginal ultrasound examination during the fifth week following embryo transfer.

Data collected for each group included the diagnosis, ovarian response, number of oocytes recovered, and fertilization and pregnancy rates per cycle. The ovarian response to different stimulation protocols in these patients was also assessed by recording the number and size of developing follicles along with the serum oestradiol and progesterone concentrations during the day of, and 2 days after, HCG administration. Dropped cycle characteristics for each patient were similarly noted. All these parameters were evaluated in all IVF cycles including those before and those after the EFS cycle. Results are reported as percentages and mean values. Statistical analysis consisted of paired Student’s t-test or χ², as appropriate, with P < 0.05 considered statistically significant.

Results

A total of 200 IVF cycles was analysed for the 35 patients. Group I patients (n = 27) underwent a total of 137 (both natural and stimulated) IVF cycles, while group II underwent a total of 63 cycles. 19.7% (n = 27) of the IVF cycles in group I and 44.4% (n = 28) of the cycles in group II (n = 8) were EFS cycles. The overall incidence of the EFS in our population was 1.8%.

The age range of the study population was from 25 to 48 years as shown in Figure 1. Comparison of both groups revealed that patients who were < 34 years of age had only one cycle of EFS with no recurrences noted. In the 17 patients who were 35 to 39 years of age, four (23.5%) had recurrence of their EFS cycles. Moreover, four of the seven patients (57%) who were ≥ 40 years of age had recurrence of their EFS cycle (Figure 1).

In the 200 cycles studied, 178 (89%) were stimulated cycles (in 24 patients) while the rest (n = 22) were natural cycles (in all 11 patients). In addition, 52 (29%) stimulated cycles were eventually dropped due to ‘poor’ ovarian response.

Several protocols were used in the induction of follicular growth (clomiphene citrate + HMG, uFSH alone, flare-up + HMG, long protocol + HMG, HMG alone) in both groups but no single protocol was related to the occurrence of single or recurrent EFS cycles in our study group.

Similarly, when the cause of infertility was evaluated with respect to recurrence of EFS cycles, no statistically significant association was noted (Table I). Most of the EFS cycles occurred in the category of tubal factor infertility, perhaps reflecting of the prevalence of tubal disease in our IVF population.

Of all the 55 EFS cycles, 13 (23.6%) occurred during the first IVF cycles, 12 (21.8%) in the second, and the rest (54.5%) in subsequent cycles (Figure 2).

Despite the fact that the number of follicles > 14 mm was not statistically different between the cycles (Table II), during the EFS cycles patients demonstrated significantly lower oestradiol concentrations than in corresponding normal IVF cycles both on the day of HCG (group I, 641.6 versus 869.1 pg/ml, P < 0.01; group II, 349.0 versus 543.8 pg/ml, P < 0.001) and 2 days later at the time of retrieval (group I, not significant; group II, 316 versus 707, P < 0.0001) (Table II).

Of the 24 patients who underwent stimulated cycles, 18 (72%) had an associated high percentage of dropped cycles. In group I, 36 cycles (in 18 patients) were dropped out of 137 cycles (26.3%), and a similar percentage was found in group II [16 cycles (in six patients) out of 63 cycles, 25.4%].

All clinical pregnancies were noted in patients who had one EFS cycle only. Out of a total of seven pregnancies, there were three livebirths, three spontaneous abortions, and one ectopic pregnancy. In those patients who had recurrence of their EFS cycles, no pregnancies were achieved.
Recurrence of empty follicle syndrome

Table II. Stimulated IVF cycle characteristics in both groups of patients

<table>
<thead>
<tr>
<th>EFS cycle</th>
<th>Group I (18 patients, 86 cycles)</th>
<th>Group II (6 patients, 40 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-empty cycle</td>
<td>EFS cycle</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>Av. no. of stimulation days</td>
<td>7.7 ± 0.9</td>
<td>8.5 ± 1.1</td>
</tr>
<tr>
<td>Av. day HCG</td>
<td>11.6 ± 1.9</td>
<td>11.2 ± 2.1</td>
</tr>
<tr>
<td>Av. oestradiol, HCG day (pg/ml)</td>
<td>641.6 ± 123.3</td>
<td>869.1 ± 201.4</td>
</tr>
<tr>
<td>Av. oestradiol, 2nd day (pg/ml)</td>
<td>874 ± 156.4</td>
<td>1007 ± 185.2</td>
</tr>
<tr>
<td>Av. Prog., HCG day (ng/ml)</td>
<td>0.5 ± 0.02</td>
<td>0.3 ± 0.01</td>
</tr>
<tr>
<td>Av. Prog., post HCG (ng/ml)</td>
<td>2.1 ± 0.3</td>
<td>0.3 ± 0.02</td>
</tr>
<tr>
<td>No. follicles &gt;18 mm diameter</td>
<td>1.79 ± 0.7</td>
<td>1.98 ± 0.6</td>
</tr>
<tr>
<td>No. follicles &gt;14 mm diameter</td>
<td>2.67 ± 0.9</td>
<td>3.2 ± 1.0</td>
</tr>
<tr>
<td>Mean no. oocytes retrieved</td>
<td>–</td>
<td>4.1 ± 1.3</td>
</tr>
<tr>
<td>Mean no. fertilized eggs</td>
<td>–</td>
<td>2.6 ± 0.7</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.
*Statistically significant.
HCG = human chorionic gonadotrophin; Av. = average; Prog. = progesterone.

Discussion

The reported incidence for the infrequent event of EFS varies between 2 and 7% (Ben-Shlomo et al., 1991), although in our series was 1.8%. Despite being a rare phenomenon, EFS has profound implications for counselling about the future reproductive performance of the couple, especially when the chances of recurrence are high, such as in advanced age patients.

We have estimated that patients with one EFS cycle have a 20% risk of recurrence in later IVF cycles (i.e. seven out of the 35 patients entered in the study suffered EFS in the subsequent cycle), and those patients with more than one EFS cycle had a poor success rate overall. The risk of recurrence is higher as the age of the patient increases, as shown in Figure 1. In our series, only sporadic events were found in patients <35 years of age, with a risk of recurrence of 24% for those between 35 and 39 years of age, and 57% for those >40 years. These data suggest that ovarian ageing, possibly through altered folliculogenesis, may be involved in the aetiology of EFS, and especially in its recurrence.

The mean number of IVF cycles in groups I and II were 5 (137/27) and 8 (63/8) respectively. These are rather high and would suggest that these women intrinsically have poor prognosis as indicated by the high number of unsuccessful IVF cycles and pregnancy rates per started cycle of 5% (7/137) and 0% in groups I and II respectively. However, we could not identify the women at risk of unsuccessful IVF.

Altered folliculogenesis is likely to be involved in the aetiology of the EFS (Meniru and Craft, 1997). Early oocyte atresia or a strong attachment of the OCC to the follicle wall were previously suggested (Tsuiki et al., 1988) as possibilities. Follicular growth and rupture lead to OCC detachment from the granulosa cells and connective tissue of the follicle. In IVF cycles, oocyte retrieval is performed just before follicular rupture. If the number and growth of developing follicles as well as plasma oestrogen concentrations show a normal response, one could speculate that failed oocyte retrieval may be due to dysfunctional intrafollicular events, such as the softening of OCC anchoring elements (Zegers-Hochschild et al., 1995; Meniru and Craft, 1997).

Ovarian ageing is linked to altered granulosa cell function (Pellicer et al., 1995), apoptosis (Jurisicova et al., 1998), and hence reduced oestradiol concentrations (Pellicer et al., 1995). We found that patients with EFS in group I showed significantly lower oestradiol concentrations on the day of HCG when compared with control cycles in the same patients, suggesting an altered granulosa cell function and metabolism. Interestingly, this finding was also significant 2 days later, at the time of oocyte retrieval, but only in patients with recurrent EFS. Different numbers of mature, oestradiol-producing follicles could partially explain these differences. However, as shown in Table II, the number of follicles >14 mm was not significantly different between the EFS and normal cycles. The other plausible explanation is a hampered granulosa cell function and/or metabolism, which reflects altered oocyte growth and maturation, and consequently EFS. It should be noted that other factors besides ovarian ageing may be involved, as 16 out of 24 patients over 34 years did not have a recurrence.

As ovarian ageing is clearly linked to low response in IVF cycles (Pellicer et al., 1995), and if our hypothesis is correct, a possible relationship might exist between poor ovarian response and failure to retrieve oocytes. We found poor response in 29% of the stimulated cycles. This is in accordance with previous findings (Ben-Shlomo et al., 1991). It was thus first suggested (Ben-Shlomo et al., 1991) that EFS in some cases could represent an advanced stage of ovarian ageing. In these cases, ovarian granulosa cells may respond to exogenous gonadotrophins with increasing oestradiol concentrations, although mature oocytes are no longer retrievable.

The release of OCC requires perfectly coordinated LH surge (or HCG as a substitute), so that meiosis may resume and, subsequently, ovulation may occur. Inappropriate timing of HCG administration may thus result in an istrogenic EFS (Khalaf and Braude, 1997). Curing this type of EFS is rather easily achieved with adequately timed HCG administration and oocyte retrieval (Khalaf and Braude, 1997). Recently, it
was suggested (Meniru and Craft, 1997) that inadequate pre-ovulatory changes in the follicles may impair the OCC detachment from the follicle wall. Accordingly, the patient described in the report (Meniru and Craft, 1997) received two doses of HCG: the first one raised plasma progesterone concentration, but no oocytes were retrieved from those follicles punctured. Twenty-four hours after repeat HCG injection, 20 oocytes were then retrieved, and a viable pregnancy was obtained, which demonstrates the viability of these oocytes. Other authors (Hassan et al., 1998) have reported similar results, suggesting that some patients may need a longer exposure to HCG in order for their OCC to detach from the follicle wall.

Other authors have suggested that a low bioavailability of administered HCG may be the cause of this syndrome (Zegers-Hochschild et al., 1995; Ndukwe et al., 1996, 1997; Ubaldi et al., 1997). The possibility of an intrinsic defect in the in vivo biological activity of some batches of the commercially available HCG is favoured (Zegers-Hochschild et al., 1995; Ndukwe et al., 1997). However, recent evidence from (Ubaldi et al., 1997) showing a rise in serum progesterone suggests that biological inactivity of the injected preparation may not explain all cases as postulated previously (Zegers-Hochschild et al., 1995; Ndukwe et al., 1997). The possibility of a problem with drug administration as a cause of such low bioavailability was similarly excluded (Ndukwe et al., 1997) when careful investigation of all cases showed that HCG was administered correctly and at the appropriate time. An intrinsic liver problem was similarly ruled out as an appropriate rise in serum β-HCG was noted following the administration of exogenous HCG from a different batch in those same patients that previously showed an EFS cycle (Ndukwe et al., 1997). A recent report (Awonuga et al., 1998) detailed four cycles in three patients with EFS where the β-HCG concentration was within the normal range on the day of oocyte recovery. Therefore, normal bioavailability of β-HCG does not exclude the diagnosis of EFS, as suggested previously (Zegers-Hochschild et al., 1995; Ndukwe et al., 1996).

Implantation may be impaired in patients with sporadically occurring EFS, as pregnancies achieved in this group were below normally expected rates (seven pregnancies in 137 cycles in group I patients). Additionally, those patients with recurrent cycles of EFS are likely to have advanced age, poor response, dropped cycles, and diminished pregnancy rate, so that oocyte donation might be their best option for conception.

Whatever the underlying cause of an EFS cycle, patients with an EFS cycle should be counselled regarding the possibility of recurrence of such an event in future cycles. Care should also be taken, during future oocyte retrievals from these patients, to aspirate some of the follicles initially and, if no OCC are noted, then proceed with a another retrieval attempt following administration of a second dose of HCG as previously reported by several authors (Meniru and Craft, 1997; Ndukwe et al., 1997; Ubaldi et al., 1997).

Acknowledgement

J.A.G.-V. is a postdoctoral research fellow supported in part by FIS 98/5051.

References


Received on April 26, 1999; accepted on February 7, 2000