The use of laparoscopic ovarian electrocautery in preventing cancellation of in-vitro fertilization treatment cycles due to risk of ovarian hyperstimulation syndrome in women with polycystic ovaries

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Fifty women with polycystic ovaries took part in a prospective randomized study. All women required treatment by in-vitro fertilization (IVF) for reasons other than anovulation. They had all previously undergone ovarian stimulation with gonadotrophin therapy which had failed to result in pregnancy or had been abandoned due to high risk of developing ovarian hyperstimulation syndrome (OHSS). Twenty-five women were treated by long-term pituitary desensitization followed by gonadotrophin therapy, oocyte retrieval and embryo transfer (group 1). Twenty-five women underwent laparoscopic ovarian electrocautery after pituitary desensitization followed by gonadotrophin therapy, oocyte retrieval and embryo transfer (group 2). A significantly higher number of women in group 1 had to have the treatment cycle abandoned due to impending or actual OHSS, determined by endocrine and clinical findings. In addition, the development of moderate or severe OHSS in completed cycles was higher in group 1. The pregnancy rate and miscarriage rates in the two treatment groups were similar. The authors propose that laparoscopic ovarian electrocautery is a potentially useful treatment for women who have previously had an IVF treatment cycle cancelled due to risk of OHSS or who have suffered OHSS in a previous treatment cycle.

Key words: in-vitro fertilization/ovarian electrocautery/ovarian hyperstimulation syndrome/polycystic ovaries

Introduction
The major complication of ovarian stimulation with gonadotrophin therapy is ovarian hyperstimulation syndrome (OHSS). Its development is associated with considerable morbidity, ranging from nausea and abdominal discomfort to ascites, pleural effusion, ovarian torsion, thrombosis, renal failure and, rarely, death (Rizk and Aboulghar, 1991). In view of the potentially serious consequences of OHSS, if moderate or severe OHSS is anticipated, the ovarian stimulation cycle is usually abandoned in order to minimize the chance of its development. Between 0.6 and 8.4% of treatment cycles are complicated by OHSS (Rizk and Smith, 1992), reflecting the variation in criteria for its diagnosis in different infertility units.

Women with polycystic ovaries undergoing ovarian stimulation as part of an in-vitro fertilization (IVF) and embryo transfer programme are considered to be at increased risk of developing OHSS (Schenker and Weinstein, 1978; Charbonnel et al., 1987) and are consequently at greater risk of having the IVF-embryo transfer treatment cycle abandoned. A past history of OHSS is a further risk factor for developing OHSS. An abandoned treatment cycle is distressing for the woman and is expensive in terms of cost and time. The clinician is aware that women with polycystic ovary syndrome (PCOS) have an unpredictable follicular response to gonadotrophin therapy. They had all previously undergone ovarian stimulation with gonadotrophin therapy which had failed to result in pregnancy or had been abandoned due to impending or actual OHSS, determined by endocrine and clinical findings. In addition, the development of moderate or severe OHSS in completed cycles was higher in group 1. The pregnancy rate and miscarriage rates in the two treatment groups were similar. The authors propose that laparoscopic ovarian electrocautery is a potentially useful treatment for women who have previously had an IVF treatment cycle cancelled due to risk of OHSS or who have suffered OHSS in a previous treatment cycle.

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Women with polycystic ovaries undergoing ovarian stimulation as part of an in-vitro fertilization (IVF) and embryo
implantation rates compared with women with normal LH values (Stanger and Yovich, 1985).

There is some evidence that correction of serum LH with normal or low concentrations using gonadotrophin releasing hormone analogues (GnRHa) does not reduce the miscarriage rate (Abdel Gadir et al., 1992), although this has been disputed (Balen et al., 1993). The use of ‘pure’ follicle stimulating hormone (FSH) or GnRHα does not reduce the incidence of OHSS (Wang and Gemzell, 1980). Treatment of anovulation with LOE is associated with a return to ovulatory cycles and conception (Donesky and Adashi, 1995) and has been favourably compared with gonadotrophin therapy in terms of ovulation and conception (Abdel Gadir et al., 1990). Further, LOE is not associated with OHSS or increased multiple pregnancy and there is a suggestion that the miscarriage rate for women with PCOS is reduced (Abdel Gadir et al., 1990).

The mechanism of action of LOE is not clear, but it would seem to manipulate the intra-ovarian endocrine environment, leading to a return to ovulation. Theories include rupture of androgen-rich cysts in the ovary, destruction of androgen-producing stroma or disruption of the thickened ovarian capsule allowing ovulation (Vaughan Williams, 1990).

In view of the potential benefits of LOE in reducing miscarriage rates, and the correction of the endocrine profile, which may have an effect upon oocyte maturation, a prospective randomized study of 50 women with PCOS undergoing IVF–embryo transfer was carried out, in order to assess the potential role of LOE. Clinical, ultrasound, endocrine and embryological data were measured. In this paper, the effect of LOE in relation to OHSS and treatment outcome will be considered.

### Materials and methods

#### Subjects

Women were recruited from the Cardiff Assisted Reproduction Unit (C.A.R.U.), a tertiary referral for infertility with an established IVF–embryo transfer programme. The study was approved by the Local Research and Ethics committee. Oral and written information as to the nature of the study was provided and written consent obtained from those women agreeing to participate. Women were excluded from the study if they were over 40 years of age, had a history of more than two miscarriages, or there was severe male factor infertility.

All women had an ultrasonic diagnosis of PCOS as described by Polson et al., 1988, and required infertility treatment by IVF–embryo transfer for reasons other than anovulation, i.e. either tubal damage or unexplained infertility. They had all previously had at least one unsuccessful ovarian stimulation cycle with gonadotrophins. This was due to poor response to stimulation whereby there was no follicular response using the step-up regime of increasing gonadotrophins over a period of 14 days, to abandonment of the cycle due to risk of developing OHSS, to development of OHSS or because the treatment was simply unsuccessful.

The value of using hormone abnormalities in the diagnosis of PCOS has been reviewed (Clayton et al., 1991). Elevated LH or a raised LH:FSH ratio are insensitive markers of a biochemical diagnosis of PCOS. Similarly, 20–30% of women with PCOS do not have any androgen excess. As these endocrine changes are not invariably abnormal in women with PCOS, they were not used as specific inclusion criteria for the study.

#### Treatment protocol

All women underwent pituitary desensitization with buserelin (Hoechst UK Limited, Hounslow, Middlesex, UK) 500 µg s.c. daily commencing on day 21 of the preceding cycle. After the next menses, women were randomized to one of two treatment groups:

- **Group 1:** conventional IVF. The dose of buserelin was reduced to 200 µg s.c. daily and ovarian stimulation commenced with human menopausal gonadotrophins (HMG) (Pergonal; Serono UK Limited, Welwyn, Herts, UK) 150 IU i.m. daily.
- **Group 2:** ovarian electrocautery and subsequent IVF. The dose of buserelin was reduced to 200 µg s.c. daily. LOE was carried out using the guarded coagulation needle (Karl Storz, W. Germany), creating a grid of holes 10 mm apart on the surface of the ovary. Care was taken to pass the needle perpendicular to the surface of the ovary to minimize further adhesion formation. The number of holes drilled depended on the size of the ovary. The technique has been previously described (Abdel Gadir et al., 1990). One week later, ovarian stimulation was commenced as in group 1. The time span from operation to commencing gonadotrophin therapy was chosen because the endocrine changes as a result of LOE occur within the first 7 days of treatment (Abdel Gadir et al., 1990) and the patients had sufficient time to recover from the procedure.

Both groups underwent serial transvaginal ultrasound follicular tracking. When three or more follicles reached an average diameter of 18 mm with an endometrial thickness of at least 8 mm, ovulation was induced with human chorionic gonadotrophin (HCG) (Profasi, Serono UK Limited) 10 000 IU i.m. Oocyte retrieval was carried out 34–36 h later. Up to three fertilized oocytes were transferred into the uterine cavity after 48–54 h.

#### Outcome measures

Clinical, embryological, ultrasound and endocrine data were recorded for each patient throughout the treatment cycle. A completed cycle was one in which the treatment proceeded to oocyte retrieval. The number of cycles abandoned in order to avoid development of OHSS was recorded with the accompanying circumstances. The pregnancy and miscarriage rate was noted along with the development of moderate or severe OHSS.

During ovarian stimulation with HMG, those women considered at high risk of developing OHSS as a result of gonadotrophin stimulation had their treatment cycle abandoned. The criteria for withholding HCG and abandoning a treatment cycle, in order to avoid the development of OHSS, vary between IVF–embryo transfer centres. Each patient must be judged on an individual basis, based upon their clinical signs and symptoms, pelvic ultrasonographic findings and serum oestradiol concentrations. In this study, the clinical signs and symptoms included nausea and/or vomiting and abdominal discomfort and distension. Ultrasound criteria included the development of >20 follicles, with a large number of intermediate and small diameter follicles, a pattern thought to be associated with development of OHSS (Blankstein et al., 1987). Other ultrasound findings of note were pelvic ascites and ovarian size. In different studies, the serum oestradiol concentration above which the withholding of HCG was recommended to prevent development of OHSS ranged from 2900 to 14 680 pmol/l (Schenker and Weinstein, 1978; Haning et al., 1983). In this study, a patient with a serum oestradiol level >10 000 pmol/l was considered to be at high risk of OHSS and the option of abandoning the treatment cycle was seriously considered. There is no single endocrine or ultrasonographic test which reliably predicts the development of OHSS, and the decision to abandon a treatment cycle required some clinical assessment, which opened the study to bias. Therefore, the final decision to abandon a treatment cycle was
Table I. Basic clinical characteristics of the women in each treatment group

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25) Conventional IVF</th>
<th>Group 2 (n = 25) Laparoscopic ovarian electrocautery + IVF-embryo transfer</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)*</td>
<td>31.0 (29.8–32.2)</td>
<td>31.8 (30.3–33.2)</td>
<td></td>
</tr>
<tr>
<td>Duration of infertility (years)*</td>
<td>8.1 (6.5–9.7)</td>
<td>8.2 (6.9–9.5)</td>
<td>0.046</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>27.7 (25.3–30.1)</td>
<td>25.7 (24.4–27.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>Previous cycle abandoned</td>
<td>3/25</td>
<td>9/25</td>
<td></td>
</tr>
<tr>
<td>Previous OHSS (moderate/severe)</td>
<td>6/25</td>
<td>14/25</td>
<td></td>
</tr>
</tbody>
</table>

*Mean value with 95% confidence interval in parentheses.

made by the clinical director of the infertility clinic who was unaware of the treatment group to which the woman had been randomized.

Patients who developed OHSS were classified as mild, moderate or severe based on clinical and ultrasound findings (Golan et al., 1989). Mild OHSS was considered a consequence of ovarian stimulation with HMG and as such was not considered a cause for concern.

Statistics

The data were analysed using the Statistical Package for Social Studies computer programme (SPSS, version 6.0, 1993). Previous and present treatment cycle outcome for the parameters studied in the two treatment groups were compared using the χ² test or Fisher’s exact test. Mean values and 95% confidence intervals were evaluated for the patients’ age (years), body mass index (BMI; kg/m²) and duration of infertility (years) in each treatment group.

Results

In all, 50 women were randomized into the study, using a blocked method of randomization, thus giving 25 in each treatment group. They were matched for age, duration of fertility and body mass index as shown in Table I. There was a larger number of women in group 2 with a past history of an abandoned treatment cycle or OHSS compared with group 1, and this difference was statistically significant (Table I).

Complications of LOE

LOE was performed as a day case. There was one case of infection in the sub-umbilical incision through which the laparoscope was passed, which responded to antibiotic therapy. The only complication as a direct result of LOE was a para-ovarian haematoma which developed after the operation had been completed. The woman was admitted to hospital with abdominal pain which resolved without treatment overnight. An ultrasound scan revealed a small haematoma adjacent to the right ovary. Ovarian stimulation was delayed 1 week by which time the haematoma absorbed. The women achieved pregnancy and had a livebirth at term.

Abandoned cycles

Five women in group 1 had their treatment cycle abandoned, being considered at too high a risk of OHSS to continue ovarian stimulation.

Case 1: abandoned on day 10 of HMG. Serum oestradiol 16 600 pmol/l, 70 follicles on ultrasound scan.

Case two: abandoned on day 13 of HMG. Serum oestradiol 23 800 pmol/l, 37 follicles on ultrasound scan.

Case three: abandoned on day 8 of HMG. Serum oestradiol 13 320 pmol/l, 45 follicles on ultrasound scan. Pelvic ascites present.

Case four: abandoned on day 10 of HMG. Serum oestradiol 17 600 pmol/l, 35 follicles on ultrasound scan.

Case five: abandoned on day 13 of HMG. Serum oestradiol 13 900 pmol/l, 60 follicles on ultrasound scan. Pelvic ascites present.

A further case in group 1 was abandoned after 16 days of HMG stimulation due to poor follicular response with a total of 55 follicles in the ovaries, all >14 mm in diameter.

Development of OHSS

In addition to the abandoned treatment cycles, four women in group 1 and one woman in group 2 developed moderate OHSS following embryo transfer, with abdominal pain, enlarged ovaries and pelvic ascites. All these women were managed conservatively with serial pelvic ultrasonography and assessment of haematocrit and urea and electrolytes to monitor their condition. None required hospital admission.

Pregnancy and miscarriage rates

The pregnancy rate per cycle commenced and per embryo transfer, and the miscarriage rates in each treatment group were similar with no statistically significant difference. The data are presented in Table II. A total of 17 pregnancies was achieved in the study, giving an overall pregnancy rate per cycle of 34%. There was a total of six miscarriages, giving a miscarriage rate of 35%.

In group 1, there was one case of failed fertilization. Six treatment cycles were abandoned, leaving 18 treatment cycles proceeding to embryo transfer. Of the miscarriages, there were two biochemical pregnancies and there was one blighted ovum at 6 weeks gestation.

In group 2, there were three cases of failed fertilization. One woman refused a fresh embryo transfer as she was fearful of developing OHSS as she had done in her previous cycle, despite there being no clinical or ultrasound evidence of OHSS and thus no reason not to proceed. Thus, overall, 21 treatment cycles proceeded to embryo transfer. There was one biochemical pregnancy, one missed miscarriage at 8 weeks gestation and one spontaneous miscarriage of monozygotic twins at 8 weeks gestation.

Of the 11 livebirths, there was one set of twins in each treatment group.
Table II. Abandoned treatment cycles, development of OHSS, pregnancy and miscarriage rates in each treatment group

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle abandoned due to OHSS risk</td>
<td>5</td>
<td>0</td>
<td>0.025</td>
</tr>
<tr>
<td>Cycle abandoned due to poor response</td>
<td>1</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Moderate OHSS</td>
<td>4</td>
<td>1</td>
<td>0.174</td>
</tr>
<tr>
<td>Mean number of oocytes collected</td>
<td>7.37</td>
<td>10.28</td>
<td></td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>76.4</td>
<td>46.0</td>
<td></td>
</tr>
<tr>
<td>Mean number of embryos transferred</td>
<td>2.5</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate/cycle</td>
<td>8/25 (32.0)</td>
<td>9/25 (36.0)</td>
<td>0.765</td>
</tr>
<tr>
<td>Pregnancy rate/embryo transfer</td>
<td>8/18</td>
<td>9/21</td>
<td>0.921</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>3/8</td>
<td>3/9</td>
<td>0.627</td>
</tr>
</tbody>
</table>

Discussion

In view of the potential morbidity, OHSS is the major concern for the clinician who treats women with PCOS by IVF–embryo transfer. If the treatment cycle is abandoned, the usual management is to treat the woman with a lower dose of gonadotrophin therapy. Such is the unpredictable nature of the response of the polycystic ovary to stimulation that this may result in a poor follicular response or further OHSS, both of which may lead to the treatment cycle again being abandoned. This study has shown that LOE can significantly reduce the chance of an IVF–embryo transfer treatment cycle being abandoned in order to prevent the development of OHSS (P = 0.025). This finding is all the more important as the women in group 2 were a more difficult sample on whom to carry out controlled ovarian stimulation without development of OHSS. Although the women were randomized into the study, there was a statistically significantly larger number of women in group 2 who had previously had an abandoned treatment cycle or had developed moderate or severe OHSS compared with women in group 1 (P = 0.46 and P = 0.021 respectively). All nine women in group 2 who had previously had an abandoned treatment cycle in order to try to avoid OHSS, had a completed IVF–embryo transfer cycle when pre-treated with LOE. Further, of those cycles which were completed, the incidence of moderate or severe OHSS was lower in those women pre-treated with LOE, but this difference was not statistically significant. There was no significant difference in pregnancy rate between the two treatment groups. The miscarriage rate in women with PCOS is high compared with the normal population, in the range of 33–40%. This was the experience in this study, although the numbers are small. The data do not concur with other studies which suggest that long term pituitary desensitization with GnRHa, to suppress serum LH, or LOE can lead to a lower miscarriage rate (Abdel Gadir et al., 1990; Balen et al., 1993). The problem of the high miscarriage rate in women with PCOS requires further investigation.

To the authors’ knowledge, this is the first prospective randomized study considering the use of LOE for women with PCOS undergoing IVF–embryo transfer in order to minimize the need to abandon treatment and limit the development of OHSS. Ovarian electrocautery involves a general anaesthetic and laparoscopy with their attendant complications. It is also an expensive procedure, adding to the already high cost of assisted reproduction. In this study, the only complication encountered as a direct result of ovarian electrocautery itself was a broad ligament haematoma which required no treatment, but this is not to say that the procedure is without complication, especially as many of these women had tubal damage and pelvic adhesions as a cause of infertility. Careless use of electrocautery may result in damage to bladder, bowel or large blood vessels.

In view of the surgical risks and the additional cost of LOE, and the fact that by far the majority of women with PCOS undergoing IVF–embryo transfer complete the treatment cycle, the potential benefit of the procedure should be carefully considered. Even in those women who have an IVF–embryo transfer treatment cycle abandoned for risk of OHSS, the majority proceed to IVF–embryo transfer in a subsequent treatment cycle. On this basis, LOE cannot be recommended as a first line treatment for women with PCOS undergoing IVF–embryo transfer. LOE is best reserved for women who have previously had at least one treatment cycle abandoned for risk of OHSS, and then after discussion of the procedure with the woman.

Acknowledgements

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References


