Low-dose dexamethasone augments the ovarian response to exogenous gonadotrophins leading to a reduction in cycle cancellation rate in a standard IVF programme

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BACKGROUND: Cancellation of assisted conception cycles because of poor ovarian response to gonadotrophins is a significant problem in assisted reproduction. Various adjuvant treatments have been suggested to improve responsiveness. This study reports on the potential benefits of low dose dexamethasone. METHODS: Patients <40 years of age were invited to participate in a twin centre prospective double blind randomized placebo controlled study. A total of 290 patients were recruited and computer randomized using sealed envelopes to receive either 1 mg dexamethasone (n = 145) or placebo tablets (n = 145) in addition to a standard long protocol gonadotrophin-releasing hormone analogue with gonadotrophin stimulation regime. RESULTS: A significantly lower cancellation rate for poor ovarian response was observed in the dexamethasone group compared with controls (2.8 versus 12.4% respectively, P < 0.002). Further comparisons between the dexamethasone group and controls were made of median fertilization rates (60 versus 61% respectively, NS), implantation rates (16.3 versus 11.6% respectively, NS) and pregnancy rate per cycle started (26.9 versus 17.2%, NS). The benefit was apparent in patients both with polycystic and normal ovaries. CONCLUSION: Low dose dexamethasone co-treatment reduces the incidence of poor ovarian response. It may increase clinical pregnancy rates and should be considered for inclusion in stimulation regimes to optimize ovarian response.

Key words: dexamethasone co-treatment/gonadotrophins/IVF/ovarian stimulation/poor response

Introduction

Poor ovarian response to gonadotrophin stimulation occurs in 9–26% of cycles initiated (Keay et al., 1997), adversely affects subsequent treatment cycles (Jenkins et al., 1991) and is not simply overcome by using higher gonadotrophin doses (Land et al., 1996). Advanced age, previous ovarian surgery, pelvic adhesions and high body mass index (BMI) have all been associated with poor ovarian response but unexpected poor responses may occur in young women (Keay et al., 1997, Keay et al., 1998a). Serum growth hormone (GH) concentrations in both natural cycles (Potashnik et al., 1995) and during controlled ovarian stimulation (Stone and Marrs, 1992) predict ovarian response, while inadequate somatotropic axis stimulation may result in poor response (Homburg and Ostergaard, 1995). The ovarian response to gonadotrophin stimulation is modulated by insulin-like growth factor 1 (IGF-1) which acts synergistically in vitro with FSH (Adashi et al., 1985) through granulosa cell receptors (Gates et al., 1987).

GH (Homburg and Ostergaard, 1995), l-arginine (Battaglia et al., 1999) and pyridostigmine (Kim et al., 1999) have been investigated as adjuvant treatments in poor responder patients. All three adjuvant treatments influenced the somatotropic axis and both l-arginine and pyridostigmine significantly improved the ovarian response, increasing endogenous GH secretion and raising intrafollicular IGF-1 concentrations.

Glucocorticoids also stimulate GH (Casaneuva et al., 1990) and IGF-1 secretion (Miell et al., 1993) and a higher IVF pregnancy rate was observed with prednisolone co-treatment compared with controls (Kemeter and Feichtinger, 1986). However, no benefit was observed with glucocorticoid co-treatment in pituitary desensitized IVF cycles (Bider et al., 1996).

The aim of this study was to determine specifically whether dexamethasone co-treatment alters ovarian responsiveness to gonadotrophin stimulation and influences IVF outcome.

Materials and methods

Patients and Protocols

The study was conducted in two University IVF centres with local medical research ethics committee approval. Patients undergoing
gonadotrophin stimulation prior to IVF were invited to participate whether or not they had previously undergone an IVF cycle. Women ≥40 years of age, taking concurrent corticosteroids or with a medical history of insulin dependent diabetes mellitus or peptic ulceration were not eligible for inclusion. All patients underwent a single cycle of treatment during the study.

Based on pilot data, power analysis determined that for a type I error of 5% and a power of 90%, 260 patients (130 in each arm) would be required to confirm a reduction in cycle cancellation for poor response, the primary end point, from 14% with placebo to 2.3% with dexamethasone. Poor response accounts for between 9–26% of cycles initiated (Keay et al., 1997) and the expected incidence in the placebo group falls within this range.

**Stimulation protocol**

**Centre A (University of Bristol)**

The stimulation protocol and laboratory methods have been described in detail previously (Keay et al., 1998b). Suppression of pituitary gonadotrophin secretion with buserelin (by nasal spray) was started in the mid-luteal phase of the preceding ovarian cycle. Patients commenced norethisterone, 5 mg twice daily for 7 days, two days prior to buserelin to reduce the chance of cyst formation. Once ovarian suppression was confirmed by serum oestradiol, ovarian stimulation was started using an s.c. injection of 150 IU purified FSH (Metrodin High Purity Urofollitrophin; Serono Laboratories, Welwyn Garden City, UK). The dose was increased after 7 days, if necessary, to a maximum of 300 IU. Ovarian follicular development was monitored by vaginal ultrasonography and serum oestradiol measurement. Human chorionic gonadotrophin (HCG) (Profasi; Serono Laboratories) was injected and oocyte retrieval undertaken if ≥3 follicles of 18 mm were recruited with a serum oestradiol concentration of 800 pmol/l per large follicle.

In addition to the above, two tablets were added each night at 2200 h of either dexamethasone 0.5 mg (Organon Pharmaceuticals, Cambridge, UK) or matching placebo (400 µg folic acid [Organon Pharmaceuticals]) commencing on the first day of gonadotrophin administration until the night before oocyte retrieval. Cycles in which less than three pre-ovulatory follicles developed did not proceed to treatment until the night before oocyte retrieval. Cycles in which less than three pre-ovulatory follicles developed did not proceed to oocyte retrieval and were cancelled due to poor ovarian response. An excessive response (>30 follicles in total or serum oestradiol >15 000 pmol/l) led to cycle cancellation because of the risk of ovarian hyperstimulation syndrome (OHSS).

Clinical pregnancies were defined by ultrasound confirmation of an intrauterine gestation sac and fetal heart activity. The ultrasound appearance of the ovaries prior to treatment was recorded. Poly-cystic ovaries were strictly defined as ≥10 peripherally placed follicles 2–8 mm diameter with an increased stromal density (Polson et al., 1988).

**Centre B (University of Sheffield)**

The stimulation protocol and monitoring procedures were identical to Centre A (outlined above). The laboratory methods were similar except that intracytoplasmic sperm injection (ICSI) was not available and the gonadotrophin preparation used was human menopausal gonadotrophin (HMG) (Pergonal; Serono Laboratories).

**Assignment and masking**

Treatments randomized by computer, using the statistical package ARCUS Prostat (Medical Computers, Aughton, UK), were held in sealed envelopes in the hospital pharmacies. Randomization was in blocks of 100 within each centre to ensure equivalent numbers in each group. Patients and staff (clinical and laboratory) were blinded to the choice. Tablets, dexamethasone or placebo were dispensed in identical containers to the patients once written informed consent was obtained. Surplus tablets were returned on completion of the stimulation cycle.

**Participant flow and follow-up**

Patients were only randomized after entry into the study hence all 290 patients were included and completed the study. Clinical data including the cycle cancellation, measures of ovarian response, treatment outcome and laboratory details were recorded for each cycle and entered into a computer database for subsequent analysis.

**Analysis**

χ²-test, Student’s t-test and the Mann–Whitney U-test were used for comparison between groups as appropriate using the statistical package ARCUS Prostat (Medical Computers). A P value of < 0.05 was considered statistically significant.

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**Table I. Summary of clinical features of patients studied comparing the dexamethasone and placebo groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dexamethasone (n = 145)</th>
<th>Placebo (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean female age years (± SD)</td>
<td>32.5 (3.8)</td>
<td>32.2 (3.7)</td>
</tr>
<tr>
<td>Primary infertility (%)</td>
<td>62.7</td>
<td>64.8</td>
</tr>
<tr>
<td>Duration infertility (years)</td>
<td>5 (3–6)</td>
<td>5 (3–6)</td>
</tr>
<tr>
<td>Previous ovarian surgery (%)</td>
<td>6.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Single ovary (%)</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Basal serum FSH (IU/l)</td>
<td>6.2 (5.0–7.5)</td>
<td>6.1 (4.9–7.3)</td>
</tr>
<tr>
<td>Basal serum LH (IU/l)</td>
<td>5.0 (3.5–6.8)</td>
<td>4.8 (3.4–6.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 (21.0–24.2)</td>
<td>23.2 (21.0–24.1)</td>
</tr>
<tr>
<td>Infertility diagnosis %</td>
<td>29.0</td>
<td>31.7</td>
</tr>
<tr>
<td>Spem dysfunction</td>
<td>43.4</td>
<td>42.7</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>7.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Unexplained</td>
<td>21.4</td>
<td>17.9</td>
</tr>
<tr>
<td>Ovulatory</td>
<td>3.5</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*aMedian values with quartile ranges in parentheses.

*bPrimary and secondary diagnosis included giving a total of >100%.

BMI = body mass index. 

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**Results**

Centre A recruited 192 patients, 67 patients underwent ICSI, and 125 patients underwent IVF. Centre B recruited 98 patients all of whom underwent IVF treatment.

The patient data in Table I shows the dexamethasone and placebo groups were similar with respect to age, basal serum FSH and BMI. 19 patients in each group had previously undergone a cycle of IVF. No side effects were reported which is in keeping with previous studies using short courses of low dose glucocorticoids. Returned, unused, surplus tablets from 40 patients were counted and correlated with the expected number given the duration of stimulation.

A significantly lower cancellation rate for poor ovarian response and a trend towards a higher pregnancy rate was observed in the dexamethasone group (Table II). The cancellation rate for over-response although higher in the dexamethasone group was not statistically significant. The significantly lower cancellation rate for poor response was observed when the two centres were analysed separately.

Analysis of the 223 IVF cycles revealed significantly lower cancellation for poor response in the dexamethasone and a higher, non-significant \((P = 0.06)\), pregnancy rate per cycle initiated compared with placebo \((2.6 \text{ versus } 12.0\% \text{, } P < 0.01 \text{ and } 28.7 \text{ versus } 17.6\% \text{, NS respectively})\). Restricting the analysis to patients undergoing a first stimulation attempt, removing a potentially confounding factor from previous treatments, left 126 patients in each treatment arm. In this group, cancellation for poor response was significantly lower \((3.2 \text{ versus } 11.9\% \text{, } P < 0.01)\) and the clinical pregnancy rate per cycle initiated was significantly higher \((28.6 \text{ versus } 16.7\% \text{, } P < 0.05)\).

In cycles reaching oocyte retrieval no difference in oocyte number or total gonadotrophin dose was observed (Table III). Fertilization rates were similar and a trend towards a higher embryo implantation rate in the dexamethasone group was observed. The mean numbers of embryos transferred was identical at 2.5 in each group.

A sub-group of 31 patients with polycystic ovaries showed similar orders of difference in cycle cancellation for poor response in the dexamethasone group compared with placebo \((5.9 \text{ versus } 14.3\% \text{ respectively})\) but the difference was not statistically significant.

**Discussion**

This is the largest randomized placebo–controlled study using dexamethasone co-treatment in IVF treatment. We observed significantly more patients developing \(\geq 3\) preovulatory follicles (criterion for oocyte retrieval) with dexamethasone compared with placebo \((97.2 \text{ versus } 87.6\% \text{ respectively})\) leading to a higher pregnancy rate per cycle initiated. The aim of the study was to determine the effect of dexamethasone on

### Table II. Clinical outcome of ovarian stimulation and IVF treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cancellation rate (%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone ((n = 145))</td>
<td>Placebo ((n = 145))</td>
</tr>
<tr>
<td>Poor response</td>
<td>4/145 (2.8)</td>
<td>18/145 (12.4)</td>
</tr>
<tr>
<td>Over response</td>
<td>6/145 (4.1)</td>
<td>3/145 (2.1)</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>39/145 (26.9)</td>
<td>25/145 (17.2)</td>
</tr>
<tr>
<td>Cycles reaching oocyte retrieval</td>
<td>((n = 135))</td>
<td>((n = 124))</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>60.0 (40–75)</td>
<td>61.0 (39–79)</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>56/342 (16.3)</td>
<td>56/309 (11.6)</td>
</tr>
</tbody>
</table>

\(^a\)Using the \(\chi^2\)-test.

### Table III. Response (totals and overall ranges) to gonadotrophin stimulation in cycles reaching oocyte retrieval (OR)

<table>
<thead>
<tr>
<th>Cycles reaching OR</th>
<th>Treatment</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone ((n = 135))</td>
<td>Placebo ((n = 124))</td>
</tr>
<tr>
<td>Oocytes(^a)</td>
<td>11 (7–14)</td>
<td>10 (7–13)</td>
</tr>
<tr>
<td>Total ampoules(^a)</td>
<td>26 (22–32)</td>
<td>26 (22–34)</td>
</tr>
<tr>
<td>Days of stimulation(^a)</td>
<td>13 (11–15)</td>
<td>13 (12–15)</td>
</tr>
<tr>
<td>Cycles (\geq 50) ampoules (%)</td>
<td>3.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Cycles (\leq 5) oocytes (%)</td>
<td>14.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Embryos available(^a)</td>
<td>5 (3–7)</td>
<td>4 (3–8)</td>
</tr>
<tr>
<td>Embryos transferred(^a)</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^a\)Median values with quartile ranges in parentheses. Ampoules contain 75 IU FSH.

\(^b\)Median.
ovarian responsiveness. This trial was not sufficiently powerful to confirm differences in clinical pregnancy rate, per cycle initiated, as significant. However, analysis of first stimulation attempts identified a significantly higher clinical pregnancy rate per cycle started.

No difference with respect to potentially confounding factors for ovarian response existed between the groups. Within each centre the treatment and placebo groups received an identical gonadotrophin and stimulation protocol. In cycles proceeding to oocyte collection measures of ovarian response were similar. These beneficial effects appeared to extend to patients with polycystic ovaries and no side effects were reported.

Distinction should be drawn between ‘poor responder’ patients who can only be identified after a stimulation cycle and the occurrence of an inadequate response identified in this study. Some inadequate responses are due to a failure to reach a threshold for follicular recruitment and these women respond well to a higher stimulation dose. This contrasts with an intrinsically reduced ovarian reserve wherein the patient remains disadvantaged despite using higher gonadotrophin stimulation doses (Jenkins et al., 1991). This study suggests dexamethasone sensitizes the ovary to gonadotrophin resulting in significantly fewer inadequate responses.

The fact that glucocorticoids may sensitize the ovary to gonadotrophins is supported by a randomized controlled study of women with polycystic ovarian syndrome (PCOS) undergoing IVF (Fridstrom et al., 1999). This trial showed a trend toward higher oocyte numbers (mean 13 versus 8 in the placebo group) and lower gonadotrophin requirements with prednisolone compared with placebo. No difference in IVF outcome was observed in a study of 78 patients with isolated tubal infertility all of whom reached oocyte retrieval (Bider et al., 1996). In that study two doses of dexamethasone were compared (0.5 and 1 mg) and no placebo was used in the 24 control patients. The power calculations used in planning our study indicate that 78 patients are insufficient to detect a difference in clinical outcome.

There are a number of potential mechanisms by which dexamethasone may affect ovarian function. Dexamethasone is a substrate for the enzyme type 1 (Best et al., 1997) 11β-hydroxysteroid dehydrogenase (11β-HSD). This isozyme has been detected in luteinized human granulosa cells (Smith et al., 1997) and oocytes (Smith et al., 2000) suggesting that dexamethasone may directly influence follicular development. The developmental regulation of human 11β-HSD isozyme expression favours a high preovulatory follicular fluid cortisol concentration (Tetsuka et al., 1997) and other species require glucocorticoids for final oocyte maturation (Greeley et al., 1986).

Dexamethasone may act indirectly by increasing serum GH (Casaneuva et al., 1990), serum IGF-1 (Miell et al., 1993) and consequently follicular fluid IGF-1 concentrations. IGF-1 mRNA has not been identified in human pre-ovulatory granulosa cells and follicles appear to derive IGF-1 from the circulation (Zhou and Bondy, 1993). Lower serum IGF-1 concentrations following pituitary desensitization (Gadd et al., 1991) may account for some suboptimal responses to gonadotrophin stimulation. Dexamethasone co-treatment significantly increases serum IGF-1 in pituitary desensitized IVF cycles compared with placebo (Jenkins et al., 1994) and may overcome a relative IGF-1 deficiency. Intra-ovarian regulation of IGF-1 and its binding proteins is highly complex (Jones and Clemmons, 1995). Insulin-like Growth Factor Binding Protein 1 (IGFBP 1) gene transcription in human hepatocytes is stimulated by glucocorticoids mediated through glucocorticoid response elements and may enhance or inhibit IGF-1 action in vitro depending on culture conditions (Schweizer-Groyer et al., 1999). Investigation of the effect of dexamethasone on IGFBP 1 and IGFBP 3, the main serum carrier of IGF-1, is warranted but currently the effect of dexamethasone at the cellular level remains speculative.

Immunosuppression, leading to a favourable endometrial environment, was the rationale behind the administration of high dose glucocorticoid from embryo transfer onwards and higher implantation rates have been observed (Polak de Fried et al., 1993). In our study dexamethasone predominantly influenced ovarian response and a major endometrial effect is unlikely with the low dose used although a trend toward higher embryo implantation was observed. Glucocorticoids’ effect on the ovarian immune system is dose-dependent. They are potent inhibitors of cytokine synthesis (Lew et al., 1988), yet macrophage migration inhibitory factor (MIF) is induced at low corticosteroid concentrations effectively overcoming this inhibitory effect (Calandra et al., 1995). Alterations in cytokine profile may affect ovarian responsiveness and this has been implicated in the aetiopathogenesis of OHSS (Mathur et al., 1997).

In conclusion low-dose dexamethasone appears to be an inexpensive and safe co-treatment which should be considered for optimizing ovarian stimulation prior to assisted conception. The mechanisms by which glucocorticoids alter ovarian responsiveness remain unclear and require further investigation.

Acknowledgements

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References


Adjuvant dexamethasone and poor ovarian response


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