Comparison of ovarian response in right and left ovaries in IVF patients

Angus J.M. Thomson1,4, M. Rafet Gazvani3, Simon J. Wood1, Stephanie C. Meacock1, D. Iwan Lewis-Jones1,2 and Charles R. Kingsland1

1 Reproductive Medicine Unit, Liverpool Women’s Hospital, Crown Street, Liverpool L8 7SS, and Departments of Obstetrics and Gynaecology, 2 University of Liverpool, Liverpool and 3 University of Aberdeen, Aberdeen, UK

4 To whom correspondence should be addressed. Email: gus@doctors.org.uk

BACKGROUND: Anatomical and cyclical physiological differences exist between right and left ovaries which may affect their function and response to ovulation induction. Although authors have compared right and left ovarian response during IVF for patients with a unilateral diseased or absent ovary, no study has examined the response of normal ovaries to gonadotrophin stimulation within the same patient. We wished to determine if there were any significant differences between right and left ovarian response in patients with healthy ovaries having standard IVF treatment. METHODS: We performed a prospective observational case–controlled study in 200 consecutive IVF patients. The main outcome measures were the number of oocytes retrieved, fertilization rates, grade of embryos produced, pregnancy rates and live birth rates. RESULTS: Comparison of right versus left ovary revealed: number of oocytes 4.9 versus 4.7, percentage fertilization 61.3 versus 62.5%, percentage of grade 1 embryos 81 versus 83%, chemical pregnancy rate 33 versus 47% and live birth rate 27 versus 32% (all not significant). CONCLUSIONS: We conclude that there are no statistical differences between right and left ovarian response in IVF patients with healthy ovaries.

Keywords: IVF/ovary/ovulation induction/ovarian response

Introduction

Manipulation of ovarian function is fundamental to many aspects of reproductive medicine and assisted conception. Ovarian function in the natural menstrual cycle has been studied in some detail and both extrinsic and intrinsic factors affect side and timing of ovulation. How individual right and left ovaries respond to the artificial situation of ovulation induction or super-ovulation cycles has been less thoroughly assessed.

Study of the basic sciences shows that whilst right and left ovaries are embryologically and histologically similar, differences do exist between their venous drainage, anatomical relations and cyclical physiological control. Although both ovaries receive arterial blood supply via the ovarian arteries directly from the aorta, the venous drainage differs as the right ovarian vein drains directly to the inferior vena cava (IVC) whereas the left drains firstly to the left renal vein then to the IVC (Gray, 1973; Last, 1984). The anatomical relations of the ovaries differ in that the left ovary lies in close relation to the sigmoid colon and the right ovary is adjacent to the caecum and appendix, though it is widely accepted that the position of both ovaries is extremely variable, especially after pregnancy (Gray, 1973; Snell, 1986).

The basic endocrine control is the same for both ovaries but there are discrete inter- and intra-ovarian physiological differences controlling both follicular development and side of ovulation in each cycle. Natural cycle ovulatory characteristics have been studied in great depth in primates. It has been suggested (Wallach et al., 1973) that side of ovulation was related to menstrual cycle length, and that in shorter cycles ovulation is likely to alternate between the two ovaries whereas in longer cycles the side of successive ovulations is more difficult to predict. Further work in the Rhesus monkey has attributed the intra-ovarian control of folliculogenesis and ovulation to inter-ovarian differences in progesterone concentration (DiZerega and Hodgen, 1982). In any cycle, the formation of a dominant follicle and subsequent ovulation is likely to occur in the ovary with the lower follicular phase progesterone level, which is usually the opposite ovary to which ovulation and corpus luteum formation occurred in the preceding month. There is more recent evidence demonstrating that dominant follicle formation and hence control of ovulation is partially controlled by inhibins and activins acting as paracrine messengers (Hillier, 1991).

Intra-ovarian physiological control of side of ovulation has also been demonstrated in humans (Potashnik et al., 1987), though its relevance to ovulation induction cycles has not been fully investigated. Potashnik also made the surprising observation that in women with two healthy ovaries, ovulation
Comparison of right and left ovaries in IVF

Materials and methods

A prospective, observational, case–controlled study was initiated at the Reproductive Medicine Unit, Liverpool Women’s Hospital, Liverpool, UK. We included a total of 200 cycles of IVF treatment in 200 consecutive patients having treatment for solely tubal or unexplained infertility, over a 9 month period (April–December 1997). Patients with any male factor infertility or requiring intra-cytoplasmic sperm injection were excluded. Other excluding factors included ovarian endometriosis, previous ovarian surgery (except bilateral ovarian diathermy) or documented difficulty at oocyte retrieval e.g. due to ovarian position. Any patient could only be included once, even if they had more than one oocyte retrieval during the study period.

All patients underwent treatment following our standard IVF treatment protocol. Pituitary desensitization was achieved with gonadotrophin-releasing hormone (GnRH) analogue (nafarelin, Synarel; Searle, High Wycombe, UK) starting from day 23 of the menstrual cycle and given for 2–3 weeks, followed by ovarian stimulation with daily injections of human menopausal or recombinant gonadotrophins (Menogon; Ferring, Middlesex, UK; Follicitron alfa, Gonal-F; Serono, Welwyn Garden City, UK). Human chorionic gonadotrophin (Profasi; Serono) 5000 IU was injected when there were at least three follicles >17 mm diameter and oocyte retrieval took place 34–36 hours later.

Oocyte retrievals were performed by either consultants or fully trained clinical research fellows from the Reproductive Medicine Unit. At the time of oocyte retrieval a single or double channel collection system was utilized, starting on either side as deemed appropriate by the clinician. Having completed the collection from one ovary the collection apparatus was flushed through with media before collecting from the opposite ovary.

Oocytes from each ovary were handled separately and routine laboratory procedures were carried out as per unit protocol. Embryologists not involved with the study performed oocyte identification, grading, and insemination. Oocytes were graded for maturation by morphological parameters according to standard unit protocol modified from published grading systems (Osborne, 1993). By this protocol Grade 1 indicates mature oocytes with very expanded cumulus and well dispersed radiating corona, evenly distributed around the oocyte. Embryologists then chose, by morphological grading criteria, the best embryos for embryo transfer, 48–52 hours after oocyte retrieval. Although the embryologist recorded which ovary or ovaries the embryos originated from, this information was not given to the clinician at the time of embryo transfer.

Luteal support comprised 400 mg progesterone suppositories/pessaries (Cyclogest; Shire, Andover, UK) given twice daily for 2 weeks commencing the evening prior to embryo transfer. In the absence of menses a pregnancy test was performed 14 days after embryo transfer when a positive test confirmed a biochemical pregnancy. Clinical pregnancy was defined as the presence of an intrauterine gestation sac with identifiable fetal heart activity and subsequent live birth data was also collected.

Statistics

At the time of trial design a median number of 10 oocytes were collected from each patient with two ovaries having IVF oocyte retrieval. We performed a power calculation to estimate the number of cycles required to observe a clinically significant drop from five to four oocytes per ovary. The study should include at least 97 cycles (power 80% and α = 5%). As this was an observational rather than interventional study, we included 200 cycles to maximize the power of the study.

Statistical analysis of data was performed using SPSS (Illinois, USA) and ARCUS (Cambridge, UK) software. Related data, such as number of oocytes and percentage fertilization from each ovary, was analysed using Wilcoxon’s signed rank test. Pregnancy outcome data was tested by χ²-test.

Results

A total of 200 IVF cycles in consecutive patients with two healthy ovaries reaching oocyte retrieval were included. The
Table I. Comparison of right and left ovarian response to controlled super-ovulation

<table>
<thead>
<tr>
<th></th>
<th>Left ovary</th>
<th>Right ovary</th>
<th>(^a P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of oocytes collected</td>
<td>4.70</td>
<td>4.87</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of grade 1 oocytes (%)</td>
<td>99.3</td>
<td>99.1</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage fertilization (%)</td>
<td>62.5</td>
<td>61.3</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage cleavage (%)</td>
<td>54.6</td>
<td>54.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total no. embryos available on day of embryo transfer</td>
<td>494</td>
<td>531</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of embryos, grade 1 on day of embryo transfer</td>
<td>83</td>
<td>81</td>
<td>NS</td>
</tr>
<tr>
<td>Side from which the transferred embryos came</td>
<td>46.5</td>
<td>53.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)Statistics: Wilcoxon’s signed rank test.
NS = not significant (\(P > 0.05\)).

Table II. Pregnancy rates following embryo transfer of embryos from one or both ovaries

<table>
<thead>
<tr>
<th></th>
<th>Left ovary only ((n = 40))</th>
<th>Both ovaries ((n = 99))</th>
<th>Right ovary only ((n = 52))</th>
<th>(^a P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of embryos transferred</td>
<td>94</td>
<td>230</td>
<td>125</td>
<td>NS</td>
</tr>
<tr>
<td>Average no. of embryos transferred per patient</td>
<td>2.35</td>
<td>2.32</td>
<td>2.40</td>
<td>NS</td>
</tr>
<tr>
<td>Positive pregnancy test (%)</td>
<td>47</td>
<td>29</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>45</td>
<td>24</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>32</td>
<td>21</td>
<td>27</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)\(P\) values comparing left versus right ovaries by \(\chi^2\)-test.
NS = not significant.

The mean age of the study population was 34.3 years (range 24–43). The mean baseline FSH level taken in early follicular phase was 7.3 IU (range 1.4–18.3). The cause of infertility was stated as tubal disease in 52% (104/200), anovulatory in 10.5% (21/200), endometriosis in 11.5% (23/200) and unexplained 26% (52/100). No patients were lost to follow-up.

During the treatment cycles the mean number of ampoules of gonadotrophin received was 32 (range 10–80). At oocyte retrieval the mean number of oocytes collected was 9.7 (range 1–34). Comparing right versus left ovarian response, the number of oocytes, fertilization rates and percentage of grade-1 embryos produced was the same for both ovaries (Table I).

Embryologists chose the best embryos for embryo transfer and 54% of transferred embryos were derived from right ovaries and 46% from left (Table I). Embryo transfer did not take place in nine cases. Four had no embryo transfer due to a significant risk of ovarian hyperstimulation syndrome, so all embryos were frozen. In the other five cases there was failed fertilization. Therefore 191 women reached embryo transfer and of these 64 (33.5%) had a positive pregnancy test and 47 (24.6%) had a live birth. Although the majority of women (99) had embryos transferred from both ovaries, 40 had embryos transferred solely from the left ovary and 52 from the right. Pregnancy rates for these groups are shown in Table II; there are no significant differences between the groups.

Discussion

Despite anatomical differences and cyclical inter-ovarian differences in folliculogenesis and ovulation no studies have been published examining right and left ovarian response to superovulation in the same patient. It has been suggested that spontaneous ovulation takes place more regularly from the right rather than the left ovary (Potashnik et al., 1987; Fukuda et al., 2000). It was also found, in the latter of these studies, that following spontaneous ovulation pregnancy was more likely after ovulation from the right rather than the left ovary. This has not previously been examined in patients having IVF. Our study suggests that in IVF cycles in patients with healthy ovaries, both right and left ovaries respond similarly. Previous studies in IVF patients who have had one or other ovary removed have not assessed differences in treatment outcome according to which ovary remains.

We are aware that intra-ovarian progesterone levels play an important regulatory role in natural cycle folliculogenesis and ovulation (DiZerega and Hodgen, 1982). Furthermore, as follicular recruitment is concomitant with a rise in FSH and a fall in inhibin A (Le Nestour et al., 1993), dominant follicle formation coincides with a rise in inhibin B (Gougeon, 1996). It appears that in IVF treatment these fine regulatory processes are lost or over-ridden allowing formation of multiple mature follicles. This will be due partly to the pituitary desensitization with GnRH analogues and the necessary short delay prior to commencing stimulation, eliminating the effect of intra-ovarian progesterone differences between the ovaries. Also, the relatively high doses of exogenous FSH administered clearly nullify the usual negative feedback mechanisms found in normal folliculogenesis. However as the mechanism of dominant follicle formation is poorly understood, it is unclear how this is over-ridden.
This study shows that in patients with healthy ovaries having IVF treatment there are no significant differences between right and left ovarian response. This implies that the normal regulatory mechanisms which control normal folliculogenesis and ovulation are over-ridden by the treatment protocols employed.

References


Received on April 20, 2001; accepted on May 24, 2001