Measurement of ovarian volume by transvaginal sonography before ovulation induction with human menopausal gonadotrophin for in-vitro fertilization can predict poor response

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The study tests the hypothesis that small ovaries measured on transvaginal sonography (TVS) are associated with a poor response to ovulation induction by human menopausal gonadotrophin (HMG) for in-vitro fertilization (IVF). A total of 140 infertile patients with morphologically normal ovaries undergoing IVF was studied. The mean ovarian volume of each patient was measured on TVS before starting HMG. Subsequent routine IVF management was conducted without knowledge of the results of TVS. The mean ovarian volume was 6.3 cm³ (range 0.5–18.9, SD = 3.1). Patients (n = 17; group A) with small ovaries of <3 cm³ (i.e. overall mean volume – 1 SD) were compared to patients (n = 123; group B) with ovaries ≥3 cm³. Both groups were of similar age (mean 35.8 versus 34.4 years). Early basal FSH concentrations were increased in group A (9.5 versus 7.0 mIU/ml, P = 0.025). The cycle was abandoned before planned oocyte recovery in nine patients (52.8%) from group A and in 11 patients (8.9%) from group B because of poor response to ovulation induction (P < 0.001). Increased age and ovarian volume were associated independently with cancellation of the cycles. The remaining eight patients from group A who had oocytes retrieved required higher doses of HMG (87.5 versus 53.8 ampoules, P < 0.01), yielded fewer follicles (10.3 versus 14.5, P < 0.05) and fewer oocytes were recovered from them (6.8 versus 11.0, P < 0.05) compared with group B. There was no difference in the fertilization or pregnancy rates or the number of embryos available for transfer in either group. Our results indicate a strong association between ovarian volume and ovarian reserve. Small ovaries are associated with poor response to HMG and a very high cancellation rate during IVF. Assessment of ovarian size should be an integral part of infertility evaluation.

Key words: assisted reproduction/ovarian reserve/ovarian volume/transvaginal ultrasound

Introduction

The ability of the ovary to respond to exogenous gonadotrophin stimulation and to develop several follicles simultaneously is essential for successful in-vitro fertilization (IVF). Failure to respond, with cancellation of the cycle, is common, particularly in older women. It would be clinically and economically helpful if there were better methods for prior assessment of the likelihood of an adequate ovarian response.

The relationship between increased female age, elevated basal follicle stimulating hormone (FSH) concentrations and diminished ovarian function with a lower chance of IVF success has been established (Lee et al., 1988; Scott et al., 1989; Toner et al., 1991; Scott and Hofmann, 1995). This reduction of ovarian function or ‘reserve’ is apparently due to reduced numbers of ovarian primordial follicles, from over 250 000 at menarche to very few at the end of reproductive life. This loss accelerates around the age of 37 years and precedes the menopause by 10–12 years (Richardson et al., 1987; Faddy and Gosden, 1995). Moreover, there is variation in the number and rate of depletion of follicles. Age and regularity of menses alone are unreliable predictors of ovarian reserve. Neither do follicular phase FSH concentrations fully indicate that ovarian function is normal and unimpaired (Scott and Hofmann, 1995; Wallach, 1995).

Andolf et al. (1987) showed that ovarian size decreases in women >40 years old and that this trend is not related to parity. Higgins et al. (1989) found a dramatic drop in ovarian volume at the menopause, with the average upper limit of normal falling from 18 cm³ in premenopausal women to 8 cm³ in post-menopausal women. As transvaginal sonography (TVS) is a reasonably accurate tool for measuring ovarian volume (Saxton et al., 1990), we assessed whether measurements of ovarian volume before IVF treatment are useful in the prediction of response to ovulation induction.

Materials and methods

Subjects

A total of 279 patients undergoing ovulation induction in preparation for IVF treatment at Hammersmith Hospital, London, UK, between September and December 1995 were studied prospectively. Proliferative phase FSH concentrations were measured immediately before starting treatment in those women ≥36 years. The upper limit was regarded as 15 mIU/ml, and women with higher values were excluded from IVF treatment. All subjects were women who had regular menstrual cycles and no clinical signs of the menopause. Only those with both ovaries clearly visible on TVS were included. Women who had a previous unilateral oophorectomy or partial oophorectomy were excluded. If either ovary contained a follicle or a cyst >10 mm in diameter it was not possible to measure accurately the net ovarian volume. Consequently, these patients were excluded from this study. Women with the typical appearance of polycystic ovaries (PCO), that is >10 follicles of <9 mm diameter with hyper-echogenic stroma...
Suffered from two or more factors. Student's n (5%), endometriosis (n 5%).

### Results

**Table I. Relationship between ovarian volume, age, basal follicle stimulating hormone (FSH) and stimulation outcome. All values are means ± SEM**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles started</td>
<td>17</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.8 ± 1.1</td>
<td>34.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>FSH concentration (mIU/ml)</td>
<td>9.5 ± 0.9</td>
<td>7.0 ± 0.5</td>
<td>0.025</td>
</tr>
<tr>
<td>No. of cancelled cycles (%)</td>
<td>9 (52.9%)</td>
<td>11 (8.9%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Days of induction</td>
<td>13.0 ± 0.4</td>
<td>12.5 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Total HMG (ampoules)</td>
<td>87.4 ± 14.9</td>
<td>53.8 ± 2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak oestradiol (pmol/l)</td>
<td>4889 ± 597</td>
<td>6111 ± 237</td>
<td>NS</td>
</tr>
<tr>
<td>No. of follicles aspirated</td>
<td>10.2 ± 1.6</td>
<td>14.5 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No. of oocytes retrieved</td>
<td>6.7 ± 1.7</td>
<td>11.0 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>61.9 ± 6.0</td>
<td>52.1 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos available</td>
<td>4.3 ± 1.2</td>
<td>5.5 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>No. of pregnancies (per started cycle)</td>
<td>2 (11.8)</td>
<td>14 (11.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are for cycles with oocyte retrieval. HMG = human menopausal gonadotrophin.*

(Adams et al., 1985), were also excluded. This is because the mean ovarian volume of women with PCO is more than average (Farquhar et al., 1994; Takahashi et al., 1995). After exclusions, 140 patients aged 24–46 years (mean 34.6, SD 4.4) were eligible for the study.

### Data analysis

Statistical analysis of the data was performed by Stata statistic package (Stata Corporation, College Station, TX, USA). The relationship between mean ovarian volume, patient’s age and measurements of the ovarian response was analysed using linear logistic regression, Student’s t-test and $\chi^2$ where appropriate. $P < 0.05$ was considered statistically significant.

### Ovary volume measurement

Ovarian volume was measured 2 weeks after starting buserelin and before commencing HMG injections. A Kretz Comborn 410 ultrasound scanner (Kretz Technik, Vienna, Austria) with 5 or 7.5 MHz transvaginal transducers was used. Each ovary was measured in three planes and ovarian volume was calculated using the prolate ellipsoid formula $V = D_1 \times D_2 \times D_3 \times 0.523$, $D_1$, $D_2$ and $D_3$ being the three maximal longitudinal, antero-posterior and transverse diameters respectively. Mean ovarian volume is the mean volume calculated for both ovaries in the same individual.

### Ovulation induction protocol

Hormone treatment (Rutherford et al., 1988) was standardized for all patients, with complete pituitary desensitization with gonadotrophin-releasing hormone analogue (buserelin acetate, Suprefact; Hoechst, Hounslow, UK) for an average of 2–3 weeks. Once oestradiol concentrations were <100 pmol/l and the thickness of the endometrium was <4 mm, daily injections of human menopausal gonadotrophin (HMG, Pergonal; Serono, Welwyn Garden City, UK) were commenced. Two ampoules (150 IU) was the starting dose for women <35 years old and three ampoules (225 IU) for older women, or more for those who had a poor response in previous cycles. The dose of HMG was not influenced by prior measurements of ovarian volume, as the clinical IVF team was not aware of these data. Average, nine of them being in group A. The remaining 123 patients with ovarian volume of 0.5–3.0 cm$^3$ (group B). Altogether 20 women responded poorly to stimulation and their treatment was abandoned. Of these, 17 had a mean ovarian volume which was less than average, nine of them being in group A. The remaining 123 patients with ovarian volume of 0.5–3.0 cm$^3$ (group B). Altogether 20 women responded poorly to stimulation and their treatment was abandoned. Of these, 17 had a mean ovarian volume which was less than average, nine of them being in group A. The remaining eight (from group B) had a mean volume of 3–6.3 cm$^3$. Only three of the 20 patients whose cycles were abandoned had an ovarian volume of 3–6.3 cm$^3$ ($P < 0.01$), and in one of these cases treatment was stopped because of threatened ovarian hyperstimulation syndrome (OHSS).

There was a significant negative correlation between age and ovarian size ($r = -0.17$, $P < 0.05$). Both these factors were independently associated with cancelled cycles. Linear logistic regression analysis showed that decreased ovarian volume was more significant than increased age ($P = 0.004$ and $P = 0.058$ respectively). Very small ovaries were not seen only in older women but at all ages.

Although the average age of patients in group A was higher, the difference was not significant (35.8 versus 34.4 years; Table I). Nine of 17 patients were cancelled in group A compared to 11 of group B (52.9 versus 8.9%, $P = 0.0001$).

Mean basal FSH concentrations were above average in group A ($P = 0.025$), but all values were within what is
considered to be the normal range. Although a few women with small ovaries reached the criteria justifying an egg collection, they responded less well, required more HMG, had fewer follicles and yielded fewer oocytes. These women showed no difference in peak serum oestradiol concentrations or endometrial thickness (data not shown). Peak oestradiol concentrations and the number of oocytes retrieved were correlated in group B ($r = 0.336, P = 0.001$) but not in group A. Fertilization rate was similar in both groups and all patients proceeding to IVF in group A had at least one normal-looking embryo available for transfer.

In group B, 17 women had one ovary <3 cm$^3$. In this subgroup, one cycle was cancelled because of poor response to ovulation induction (5.9%), and the remaining 16 responded in a similar manner to women with both ovaries >3 cm$^3$.

**Discussion**

Ivarson *et al.* (1983) reported on the changes in ovarian volume during a woman’s life. They showed that mean ovarian volume increased from 0.7 cm$^3$ at age 10 years to 5.8 cm$^3$ at age 17 years. This latter volume is similar to that which we observed. It has been suggested that there are no major changes in ovarian volume during reproductive years until the premenopausal period. In menstruating women around age 40 years, there tends to be a decrease in ovarian size which is unrelated to parity. Thereafter there is a further sharp decline in size in postmenopausal women which seems mostly related to the time when menstruation ceases, rather than merely to age, because when oestrogen treatments were given, there appeared to be no observed decrease in ovarian volume with age (Andolf *et al.*, 1987).

Ovarian volume measurements are useful methods for grading the severity of OHSS (Dahl Lyons *et al.*, 1994.) Oyesanya *et al.* (1995) showed recently that total ovarian volume measured before administering HCG in IVF cycles may predict the risk of developing moderate or severe OHSS.

Gore *et al.* (1995) used ultrasonography to follow the developing follicles in fertile cycling women. They characterized individual follicles into dominant, subdominant, ovulatory and atretic categories by their size, shape, echogenicity and dynamics of growth, and demonstrated association between dominant and subdominant follicles to cycle outcome.

There are no data about the differences in ovarian volume in fertile and infertile women. Farquhar *et al.* (1994) and Takahashi *et al.* (1995) showed that PCO syndrome patients have larger ovaries than fertile control volunteers. However, several investigators reported that ~30% of PCO syndrome patients have normal ovarian volume; there is, moreover, considerable overlap between these two groups (Yeh *et al.*, 1987; Pache *et al.*, 1992). Recently, Takahashi *et al.* (1994) showed that 96% of PCO syndrome patients who had enlarged ovaries (>6.2 cm$^3$) and multiple follicles (>10 mm) failed to respond to clomiphene citrate.

Syrop *et al.* (1995) found similar results to those of our study, although they included patients with PCO. This is the first study that evaluates the significance of ovarian volume in infertile patients without PCO. The mean ovarian volume in our patients was 6.3 cm$^3$, well within the normal value for ovarian volume of women of reproductive age and similar to the value found in the control group of Takahashi *et al.* (1994, 1995). Our results show that patients with small ovaries have a cancellation rate four times that of patients with ovaries larger than the mean (20 versus 5%, $P < 0.01$). More significantly, patients with very small ovaries (i.e. <3 cm$^3$) face >50% chance that the cycle will have to be abandoned before oocyte retrieval in spite of receiving an increased daily dose of HMG. Moreover, those avoiding cancellation require more aggressive stimulation and have significantly fewer follicles and fewer oocytes.

The total number of follicles declines throughout life. Richardson *et al.* (1987) confirmed histologically that only a residue of a few hundred or thousand follicles remain by the age of 50 years. Faddy and Gosden (1995) recently used a sophisticated mathematical model which suggests that follicular exhaustion is accelerated after the age of 38 years. This precedes the clinical menopause by one decade. The ovaries become progressively less responsive to exogenous gonadotrophins, until they are totally refractory at the time of the menopause. Oddly, the ovaries cease to respond to stimulation even though some follicles still remain in the stroma. Once the ovary is more or less exhausted, increased pituitary production of FSH follows. Although elevated concentrations of FSH occur a few years before the actual menopause, monthly variations in FSH secretion mean that FSH measurement is only of very limited value in assessing the prognosis for IVF treatment. All patients with cancelled cycles could not have been identified by measurement of basal FSH alone. We confirm that decrease in ovarian volume is an earlier sign of ovarian depletion and its measurement is likely to be clinically useful. However, it is not yet clear whether the number of follicles in the ovarian cortex reflects the quality of the oocytes because fertilization and pregnancy rates were similar in both groups.

Ovarian volume measurement is quick and cost-effective. We recommend that ovarian volume should be measured by transvaginal scan before ovulation induction in all patients, regardless of age, and stimulation planned accordingly. Our results suggest that women who have a mean ovarian volume of <3 cm$^3$ have a very high chance of failure to respond to exogenously applied stimuli.

**References**


Ovarian volume and response to ovulation induction


Received on June 26, 1996; accepted on October 28, 1996