The effect of pituitary desensitization on ovarian volume measurements prior to in-vitro fertilization

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The measurement of ovarian volume has been recently shown to predict follicular response in in-vitro fertilization (IVF), specifically a lower number of retrieved oocytes with decreasing ovarian volume. This test appears to be better than basal follicle-stimulating hormone (FSH) as a prognostic measure of ovarian reserve. However, the effect of pituitary desensitization on ovarian volume has not been previously investigated. We prospectively evaluated 38 women undergoing IVF using a long luteal leuprolide acetate (LA) protocol. All women had their ovarian volume measurements performed on day 21, the day of LA start, and again on the day of gonadotrophin start. The mean age was 30.6 ± 3.9 years (range 23–37). Basal FSH was 5.4 ± 1.9 IU/l (range 1.2–10.2). The mean preLA ovarian volume was 7.0 ± 3.6 cm³ (left ovary 6.8 ± 3.9, right ovary 7.1 ± 3.8), compared to 6.3 ± 4.2 cm³ postLA (left ovary 6.0 ± 4.9, right ovary 6.5 ± 4.8) (not significant). The mean number of small antral follicles noted in both ovaries was also unchanged after pituitary desensitization. Pituitary desensitization using LA had no effect on overall ovarian volume measurements. The total number of retrieved oocytes decreased with increasing age and decreasing ovarian volume.

Key words: IVF/leuprolide acetate/ovarian volume/ultrasound

Introduction

The measurement of ovarian volume has been recently shown to predict follicular response in in-vitro fertilization (IVF), specifically a high cancellation rate, a lower number of retrieved oocytes, and lower pregnancy rates with decreasing ovarian volume (Syrop et al., 1995, 1997; Lass et al., 1997; Tomas et al., 1997). Ovarian volume also predicts ovarian hyperstimulation syndrome (Danninger et al., 1996), and is correlated with the number of small antral follicles before stimulation (Tomas et al., 1997). This test appears to be better than basal follicle-stimulating hormone (FSH) as a prognostic measure of ovarian reserve (Syrop et al., 1997). All the above studies evaluated ovarian volume either prior to initiating pituitary desensitization, or on the day of gonadotrophin start. However, the effect, if any, of pituitary desensitization on ovarian volume has not been previously investigated.

Materials and methods

Population

We prospectively evaluated 38 patients undergoing a long luteal leuprolide acetate (LA) protocol for IVF. All women had both their ovaries present, and women with prior ovarian surgery, visible endometriomas or follicles >8 mm on baseline ultrasound were excluded from the study. Women with polycystic ovaries were not excluded. It is our practice to put all women on oral contraceptives immediately prior to an IVF cycle. All patients were therefore on an oral contraceptive (Alesse®; Wyeth-Ayerst, Philadelphia, PA, USA) for at least 3 weeks (range 3–6 weeks) prior to pituitary desensitization. Oral contraceptives were withdrawn 4–5 days after LA start. All women had their ovarian volume measurements taken the day of LA start (1 mg, Lupron®; TAP Pharmaceuticals, North Chicago, IL, USA) on cycle day 21, and again on the day of gonadotrophin start after documented pituitary desensitization. Ovarian volumes were calculated only after the outcome of the IVF cycle was known, and therefore the authors were blinded to the first measurements at the time of the second ultrasound examination. The stimulation protocol was not altered based on individual measurements. Ovarian stimulation was started on the third day after a withdrawal bleed and documented pituitary desensitization using 2–4 ampoules (75 IU) of FSH and/or HMG (Metrodin® or Fertinex®; Serono, Nowell, MA, USA and Humegon®; Organon, West Orange, NJ, USA).

Fourteen women had tubal disease (36.8%), seven had male factor infertility (15.8%), six had endometriosis (15.8%), three had ovulatory dysfunction (7.8%), and four were oocyte donors (10.5%).

Ultrasound measurements

All measurements were performed using a 6.5 MHz vaginal probe (Performa®; Acoustic Imaging, Dornier Medical Systems, Phoenix, AZ, USA) by two of the authors (FIS or HDM). Ovarian volumes were calculated using the formula for an ellipsoid (0.526×length×height×width) (Syrop et al., 1995; Tomas et al., 1997). The number of small antral follicles was also recorded according to three groups: <5, 5–15, and >15 (Tomas et al., 1997). Mean ovarian volume is the mean volume calculated for both ovaries in the same individual. Patients with ovarian follicles >8 mm were excluded from the study because their ovarian volumes will be not be accurately measured.

Laboratory analysis

Basal (cycle day 3) FSH and oestradiol were performed within 2–3 months prior to the IVF cycle. For serum FSH, a microparticle enzyme immunoassay was used (Abbott Axsym system®; Abbott Pharmaceuticals, Abbott Park, IL, USA). The interassay and intra-assay coefficients of variation were 3.48% and 4.52% respectively. The upper limit of normal for FSH in our laboratory is 10 IU/l (conversion factor to SI units, 1.0), which is equivalent to 18 IU/l by
radioimmunoassay Lecco assay® (Lecco Diagnostics, Southfield, MI, USA). For oestradiol, a radioimmunoassay was used (Coat-a-count®; DPC, Los Angeles, CA, USA). The interassay and intra-assay coefficients of variation were 7.8% and 5.8%, respectively.

Statistical analysis

Data are expressed as mean ± SD. Paired t-test was used to compare the ovarian volumes of the 38 patients who underwent a long luteal gonadotrophin-releasing hormone analogue (GnRHa) cycle. P was significant at <0.05. Power calculations and 95% CI were performed where needed.

Results

The mean age was 30.6 ± 3.9 years (range 23–37). Basal FSH was 5.4 ± 1.9 IU/l (range 1.2–10.2). Basal oestradiol was <50 pg/ml after pituitary desensitization in all 38 patients. One case of moderate OHSS was identified (mean preLA volume 8.9 cm³, mean postLA volume 13.8 cm³).

The mean ovarian volume for each patient before and after LA is shown in Figure 1. Thirteen women had an increase in their ovarian volume after LA treatment, and 25 had a decrease in their ovarian volume. The mean preLA ovarian volume was 7.0 ± 3.6 cm³ (range 2.3–15.4 cm³) (left ovary 6.8 ± 3.9 cm³, right ovary 7.1 ± 3.8 cm³), compared to a postLA ovarian volume of 6.3 ± 4.2 cm³ (range 2.3–16.4 cm³) (left ovary 6.0 ± 4.9 cm³, right ovary 6.5 ± 4.2 cm³) (P = 0.13, 95% CI: −1.54 to 0.21). Ovarian volume was related to the number of small antral follicles. Figure 2 shows the mean number of small antral follicles noted in both groups. No difference was noted in the mean number of small antral follicles pre or postLA.

Discussion

Ovarian volume is a recent and novel measure of ovarian reserve, and has been shown to be predictive of IVF outcome (Syrop et al., 1995, 1997; Danninger et al., 1996; Lass et al., 1997; Tomas et al., 1997). Specifically, women with small ovarian volumes (−1 SD) have a higher cancellation rate, higher gonadotrophin requirements, lower peak oestradiol, lower number of retrieved oocytes, and a lower pregnancy rate compared to those with normal volumes (Syrop et al., 1995, 1997; Lass et al., 1997; Tomas et al., 1997). In our study, short term pituitary desensitization appears to have no effect on ovarian volume and the number of small antral follicles, and therefore performing only one ultrasound examination on the day of LA start is sufficiently accurate in predicting the outcome. A power analysis reveals that the number of
patients needed to detect a 25% decrease in ovarian volume after LA administration using a SD of 3.0 and an 80% power is 1133. Whether a longer exposure to a GnRHα (such as exposure to a depot formulation) affects ovarian volume and the number of small antral follicles remains to be investigated.

Ovarian volume measurements are reproducible among different examiners. Interobserver and intra-observer variations in volume measurements were previously shown to be very low (4–6%) (Higgins et al., 1990; Syrop et al., 1995), potentially making ovarian volume a better test of ovarian reserve than basal FSH which can vary widely between cycles (Scott et al., 1990; Scott and Hofmann, 1995; Wallach, 1995). Most recently, Syrop and co-workers (1997) showed that combining age and the volume of the smallest ovary have a 75% sensitivity and specificity (by ROC) in predicting low numbers of retrieved oocytes in 261 cycles. These investigators also showed that clinical pregnancy was best predicted by the smallest ovarian volume and smoking status but not by basal FSH or oestradiol (Syrop et al., 1997). We did not evaluate the impact of smoking on ovarian volume because only three of our patients (12.5%) were current smokers. As noted previously, small ovarian volumes were seen in all age groups despite a normal basal FSH (Syrop et al., 1995; Lass et al., 1997). The impact, if any, of oral contraceptive pills on ovarian volume has not been investigated to date. It is unlikely that this short exposure can affect ovarian volume in a significant manner since each patient served as her own control. We are currently evaluating whether oral contraception affects ovarian volume.

In our view, ovarian volume measurements should be performed only after pretreatment with oral contraceptives to prevent the formation of follicles or cysts >8 mm. All the previous studies relating to ovarian volume measurements did not utilize oral contraceptives, and have excluded patients with follicles or cysts >10 mm in diameter (Lass et al., 1997), or >15 mm in diameter (Syrop et al., 1995). On the other hand, Danninger et al. (1996) pretreated all their patients with oral contraceptives before measuring ovarian volumes; however, they failed to mention whether they excluded any patient with follicles or cysts larger than 10 mm from their study.

In conclusion, pituitary desensitization using LA has no effect on overall ovarian volume measurements or the number of small antral follicles. Performing only one ultrasound examination to evaluate ovarian volume prior to initiating pituitary down-regulation is sufficiently accurate in predicting outcome. This information may be crucial in tailoring the stimulation protocol on an individual basis to optimize outcome.

References


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