Mean Ovarian Diameter (MOD) as a Predictor of Poor Ovarian Response

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Purpose: To determine the predictive value of mean ovarian diameter of ovarian response in controlled ovarian hyperstimulation (COH), in outcome with normal FSH level in early follicular phase of menstrual cycle.

Methods: A prospective study established the prognostic value of the mean ovarian diameter of total 57 cases, including 17 patients undergoing IVF treatment with poor ovarian response and 40 patients (control group) with adequate ovarian response.

Results: The mean ovarian diameter (MOD) of patients in the cancelled group was significantly lower (19.23 ± 2.78) than in a comparable control group (24.67 ± 3.38) [$p < 0.001$]. The mean ovarian diameter was a good predictor of poor ovarian response—area under receiver operating characteristic curve— $\text{ROC}_{\text{AUC}} = 0.88$. The best criterion value discriminating between cancelled cycle and punctured was ≤ 20.6 mm.

Conclusions: Our data demonstrate that the mean ovarian diameter provides good prognostic information in outcomes with poor ovarian response during controlled ovarian hyperstimulation in IVF. The test is easy to perform and it is a good informative resource.

KEY WORDS: COH; IVF; logistic model; MOD; poor response.

INTRODUCTION

The ovarian response to gonadotrophins in controlled ovarian hyperstimulation (COH) is sometimes difficult. Prediction of poor responder outcome represents a challenge to those carrying out assisted reproduction techniques. Low ovarian response to COH occurs in 9–18% of the cases (1).

The definition of “poor response” varies from one author to another. The original definition of low response was based on low peak estradiol level, small number of follicle and oocytes retrieve (2). Serafini *et al.* (3) defined poor responders as those producing

less than three follicles. Other authors (4) have referred to four follicles as their cut-off point, while Land *et al.* (5) abandon the cycle when less than five follicles are produced. Some authors have considered less than six follicles as a reason for cancellation in COH (6).

In spite of these differences in definition, poor response cases often lead to cycle cancellation and to another try for better response in a subsequent cycle. The availability of screening tests to identify patients with poor response to ovarian stimulation would provide physicians with a valuable means of selecting a proper treatment protocol. Tests of functional ovarian reserves can often be used to predict low response to standard protocols (7). These include basal levels of: follicle stimulation hormone (FSH), luteinizing hormone (LH), FSH: LH ratio, estradiol (E_2), inhibin B, ovarian biopsies, and follicular density assay (8–12). Other tests include dynamic ovarian reserve assessment as clomiphene citrate challenge test

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[CCCT] (13), gonadotrophin releasing hormone agonist stimulation test [GAST] (14), exogenous follicle stimulating hormone ovarian reserve test [EFORT] (15).

Ultrasonography (US) may help in predicting poor responders' cases. Measurement of ovarian volume (16), antral follicle count (18), and ovarian stromal blood flow with Doppler color (19) are promising techniques for ovarian reserve prediction. All tests considered have provided prognostic information, but sometimes it is relative.

The mean ovarian diameter (MOD) measured in the largest sagittal plane of the ovary correlates with the ovarian volume and could be used for fast assessment of the ovarian status before COH (20). The purpose of this study is to establish whether the mean ovarian diameter has a good prognostication value for evaluation of the ovarian reserve.

MATERIALS AND METHODS

Population

Between October 2001 and November 2002 was performed a perspective study. The study was approved by the local ethics review committee. The research covered 57 women who visited our center for their first cycle of controlled ovarian hyperstimulation (COH). The eligibility criteria included 20–40 years old women with regular menstrual cycle (21–35 days), presence of two ovaries, normal basal serum FSH concentration (3.5–12.5 mIU/mL), Body Mass Index (BMI)—18–27 kg/m², written informed consent. The eligibility criteria excluded endocrine abnormalities (including polycystic ovarian syndrome (PCOS) and previous exposure to gonadotrophin treatment. The causes of infertility were tubal in 9 (17%) cases; male factor in 33 (64%) cases, and unexplained in 10 (19%) cases.

Experimental Design

Between days 2 and 4 of a nonstimulated menstrual cycle, without hormonal treatment for a minimum of 3 months before the investigation, patients underwent a transvaginal ultrasound examination to measure mean ovarian diameter, as described previously (20). We measured two diameters in the largest sagittal plane of the ovary: the longest possible diameter (D_1) and the second longest possible ovarian diameter (D_2) to be at a right angle to the first measurement (Fig. 1). We calculated the mean ovarian diameter us-

ing a two-dimensional formula to evaluate ovarian size:

$$\text{MOD} = [\{\text{MOD}_{\text{leftov.}} = (D_1 + D_2)/2\} + \{\text{MOD}_{\text{rightov.}} = (D_1 + D_2)/2\}]/2.$$

Ultrasound examinations were performed by a single author (I.V.) using FF Sonic UF4500N (Fokuda Denshi, Japan) with a 5-MHz vaginal transducer.

Pituitary suppression with GnRH analogues (Decapeptyl 0.1; Ferring; Germany) was started on day 21 of the cycle. For confirmation of pituitary downregulation after agonist-induced withdrawal bleed, estradiol (E_2) serum concentration of <50 pg/mL is required. Ovarian stimulation started with a fixed daily dose of 150 IU urinary gonadotrophins (Humegon, Organon, The Netherlands). After 4 days the daily dose was adjusted individually.

Cycles were cancelled if the ovarian response was poor, i.e. <4 follicles with diameter >14 mm after 8 days of stimulation or when requirements for HCG application were not accomplished following 4–5 days.

Statistics and Probability Testing

We used the Mann Whitney U test and Student's t test as appropriate. The diagnostic accuracy, described as its ability to discriminate between patients with poor ovarian response and the control group (normal ovarian response), was assessed by the area under the receiver operating characteristic (ROC) curve. The AUC_{ROC} value model was compared using the Hanley & McNeil's method (21). The area between 1.0 and 0.5 denotes no overlapping, respectively between groups. Sensitivity, specificity, and positive predictive value were calculated at the discriminating cut-off point for the prevailing part of the studied population. Sensitivity is the percentage of abnormal cases (poor ovarian response) correctly identified as such by the diagnostic test (i.e. true positives). Specificity is the percentage of normal cases (normal ovarian response) correctly identified as such by the diagnostic test (i.e. false positives). The positive predictive value is calculated from the ROC analysis by plotting the percentage and mean probability that the poor response cases are present when the test is positive). The negative predictive value is calculated from the ROC analysis by plotting and mean probability that the poor response outcomes are not present when the test is negative.

Fig. 1. Mean ovarian diameter (MOD) using a two-dimensional formula to evaluate ovarian size: $MOD = \frac{[MOD_{left\ ov.} = (D_1 + D_2)/2] + [MOD_{right\ ov.} = (D_1 + D_2)/2]}{2}$.

The data were analyzed by using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) and MedCalc Software (Mariakker, Belgium).

RESULTS

A total of 57 COH cycles were performed in 57 couples. Seventeen patients had poor response to ovarian stimulation and 35 patients (control group) adequate response.

The age of patients ranged between 29 and 40 years with a mean age of $36.53 (\pm 3.22)$ years from the study group (cancelled cycles), while the control group of patients (noncancelled cycles) ranged between 24 and 40 years of age with a mean age of $31.86 (\pm 3.67)$ years. We found that the mean ovarian diameter of patients in the cancelled group (who produced less than four follicles) differed significantly (19.23 ± 2.78) when compared with the control group (24.67 ± 3.38) [$p < 0.001$].

The ROC analysis was used to determine the best threshold values for applying mean ovarian diameter test.

Figure 2 shows the receiver operating characteristic (ROC) curve for prediction of ovarian response by mean ovarian diameter in early follicular phase of the menstrual cycle. Using the value of 20.6 mm as the

Fig. 2. Receiver operating characteristic (ROC) curve for prediction of ovarian response by mean ovarian diameter.

cut-off point, mean ovarian diameter gives the highest prediction of 11.38 positive likelihood ratio, 76.5% sensitivity, 94.1% specificity, 88% positive predicted value, and 85% negative predictive value for ovarian response for the study group of patients. When we performed a logistic regression analysis of the mean ovarian diameter, we also found an area under receiver operating characteristic curve— $\text{ROC}_{\text{AUC}} = 0.88$ and a correct prediction—84.4%.

DISCUSSION

This study makes a review of the mean ovarian diameter test usefulness as prognostic marker for prediction of the ovarian response to COH.

Our results show that the mean ovarian diameter of patients in the cancelled group was significantly lower than that of the comparable control group [$p < 0.001$]. The mean ovarian diameter was a good predictor of poor ovarian response—($\text{ROC}_{\text{AUC}} = 0.88$). The best criterion value discriminating between cancelled cycle and punctured was ≤ 20.6 mm.

Frattarelli *et al.* (17) study has shown that the cancelled cycles to exogenous gonadotrophin stimulation are associated with statistically less ovarian size measured by mean ovarian diameter. The authors did not apply a ROC analysis, but in their opinion, the mean ovarian diameter < 20 mm was connected with a statistically significant increase of the cancelled cycles.

In our study we used a ROC analysis for diagnostic of low responsible outcome and established a cut-off point of ≤ 20.6 mm of mean ovarian diameter. Regrettably, we did not find more references to studies on the prognostic values of the mean ovarian diameter ultrasound test in cases with low ovarian response to controlled ovarian hyperstimulation.

Ovarian volume correlate with ovarian response to COH in ART cycle (22, 23). Other authors also found a correlation between ovarian volume and reproductive potential and concluded that ovarian volume might be an important predictor of ovarian reserve (24) and indirect indicator of the activity of the ovaries (25). However some data noted that an error of 2 mm in each diameter measurement would result in a 25% increase or decrease in ovarian volume in normal ovary and as much as a 50% change in the volume of the smaller postmenopausal ovary (26). Authors recommended using the largest ovarian diameter as a better biometric measurement of ovarian size.

Frattarelli *et al.* (20) found that the mean ovarian diameter measured in the two-dimensional largest sagittal plane of the ovary, calculated on the basis of two diameters formula, is a good estimation of ovarian size and correlation between MOD and three-dimensional ovarian volume evaluation is 90%.

Measurement of ovarian size by MOD provides some advantages in comparison with measurement of the largest ovarian diameter and the ovarian volume test. Mean ovarian diameter test performance is as easy as the measurement of the largest ovarian diameter, but it is more informative because two diameters are measured for determination of the ovarian size. Mean ovarian diameter test performance is easier and it lowers the risk of error in measuring the diameters than the three-dimensional formula for determination of the ovarian volume with two-dimensional ultrasonography.

The results we have obtained indicate that the mean ovarian diameter measured in the largest sagittal plane of the ovary can be used for a good and fast assessment of the ovarian status before COH. The test is easy to be applied and has a good informative value.

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