Original Article

Comparison of Ovarian volume and Antral follicle count with Endocrine tests for prediction of responsiveness in ovulation induction protocols

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Abstract

Background: The aim of this study was to determine if the basal antral follicle number and ovarian volume contributes to the prediction of responsiveness in ovulation induction protocol and comparison of it with hormonal tests.

Materials and Methods: 52 irregularly-menstruating patients, aged 18-46 years, participated in this prospective study. All the patients underwent a transvaginal sonography to measure the basal ovarian volume and the basal antral follicles count (AFC). Clomiphene citrate challenge test was measured by summation of measurements of FSH on day 2 and 10. All the women received clomiphene citrate from day 2 to 6. Ovarian responsiveness was measured 1 week after termination of clomiphene citrate and was used as gold standard.

Results: Multiple regression analysis revealed that AFC was the only significant factor for ovarian responsiveness prediction. The area under the curve for AFC to discriminate responder ovaries was 0.66 (95% confidence interval, 0.87-0.99). The cutoff value for predicting ovarian responsiveness was 15.5.

Conclusion: AFC can contribute to the prediction of responsiveness in ovulation induction protocol better than ovarian volume and hormonal tests.

Key Words: Basal antral follicle, clomiphene citrate challenge test, ovarian volume, ovulation induction, ultrasonography

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INTRODUCTION

The percentage of general population seeking help for infertility is growing.[1,2] Nowadays, pregnancy is increasingly being postponed, which leads to infertility due to diminished ovarian reserve.[3] It is generally known that reproductive aging is related to both quantitative and qualitative reduction of primordial follicle pool.[4] These facts decrease successful stimulation, clinical pregnancy, and live birth rate in women pursuing ovarian induction. Therefore, we need some easy and cheap factors to predict ovarian response to induction, before starting the time-consuming and expensive induction procedures.[5] These factors can help the clinician to divide the patients in to poor and adequate responders, and this may reduce the cancelling cycles after therapy.[6]

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In addition, we know that clomiphene has some side effects, including nausea, vomiting, flashing, [7] migraine,[8] psychotic illness such as manic delirium,[9] ovarian cancer, endometrial cancer,[10] thyroid cancer,[11] and even central retinal vein obstruction (as a case report).[12]

In the other hand, failure of treatment is associated with distress of couples who participated in this program, which have direct effect on treatment outcome. [13-15]

So, determination of predictive factors helps to select the patients who seem to have adequate responsiveness and excluding patients with poor outcomes, which will follow with additional distress and acceptance of drug side effects. Several factors have been documented to predict poor or adequate responsiveness after ovarian stimulation, which can be divided to hormonal and sonographic indices.[6]

To date, studies evaluating multiple prognostic factors are scarce or do not include the full range of prognostic factors available.[16]

These markers may have limitations of their accuracy, cost, convenience, and utility. [17]

The current study is designed to compare antral follicle count and ovarian volume measuring by ultrasound with hormonal test to predict ovarian responsiveness in ovulation induction protocols.

MATERIALS AND METHODS

In this prospective study (between November 2008-September 2009), 52 irregular-menstruating patients were enrolled, aged 18-46 years who were eligible for ovulation induction protocol. Cases were selected in simple consecutive manner.

The inclusion criteria were

(1) Showed 2 patent fallopian tubes or at least 1 patent fallopian tube with no further pathology in hysterosalpingography.
(2) Normal pelvis documented by a transvaginal ultrasound with respect to uterus, fallopian tubes, and ovaries within 3 months prior to study.
(3) Male partner with semen analysis showing acceptable values. Therefore, patients with a severe male factors, which was defined as (1) less than 1 million motile spermatozoa after Percoll centrifugation and/or, (2) > 20% antibodies present on the spermatozoa after processing with Percoll centrifugation and/or, (3) > 50% of spermatozoa without an acrosome, were not included in the study.

Untreated or insufficiently-corrected endocrinopathies, clinically relevant systemic disease, or body mass index >28 kg/m^2 were other criteria that according to them the patients were not included in this study.

The ethical committee approval was obtained in our center.

All the patients underwent transvaginal sonography to measure the basal ovarian volume and count of basal antral follicles, and clomiphene citrate challenge test (CCCT) was performed. All the cases were induced by clomiphene citrate tablets (Hormone Daroo Company) 50 mg daily for 5 days, from day 2 to day 6 of the menstrual cycle. Patients were evaluated for determination the ovarian responsiveness by transvaginal ultrasonography (TVS) 1 week after clomiphene citrate administration.

Clomiphene citrate challenge test

On 2nd day of menstrual cycle, the basal values of FSH (bFSH) and on 10th day of the menstrual cycle, the stimulated level of FSH (sFSH) were determined. CCCT was measured as the sum of bFSH and sFSH. [6]

Ovarian responsiveness was defined on transvaginal sonography as evidence of at least one follicle measuring between 18-22 mm in diameters.[6]

Transvaginal sonography

TVS was performed using concept MC ultrasound apparatus (6.5 MHZ endocavity probe).

The volume of each ovary was calculated by measuring its 3 dimensions and applying the formula for an ellipsoid: (D1 × D2 × D3 × π/6). The volumes of ovaries were added for the total basal ovarian volume (TBOV).[6]

Total antral follicle count (AFC) was defined as the sum of number of follicles in both ovaries. The follicles visualized and counted by TVS in the early follicular phase were 2-10 mm in size.[6]

Data was analyzed by SPSS-13 software. To determine the cut off points, receive operator characteristic curve was used, and with 2 dimensional tables, specificity and sensitivity for each variable was assumed. Predictability of each variable was determined by logistic regression analysis. To compare the means, independent *t*-test was used. Data were reported as minimum, maximum, and mean (SD). *P*-values less than 0.05 were considered significant.

RESULTS

In this study, 52 patients underwent clomiphene

induction protocol. In these patients, the ovarian volume ranged from 2.6 to 39.60 ml, with an average of 15.4 ml (8.2). The antral follicle count ranged from 4.0 to 45.0, with mean of 19.9 (8.7). The Clomiphene citrate challenge test results ranged from 6.4 to 41.3, with an average of 15.4 (6.3). The range of age were 20 to 46 years old, with mean of 28.7 (6.50) years old.

Positive response to ovulation induction protocol was seen in 55.8% of patients (29 cases).

The mean age in patients with positive response was 27.9 (5.7) years, and the mean age in patients with negative response was 29.6 (7.5) years. The independent t-test has shown that there was no significant difference of age between two groups (*P*-value = 0.37).

The mean of AFC in patients with positive and negative responses were 17.8 (7.4) and 22.5 (9.6), respectively. The independent t-test has shown that there was a significant difference between groups (*P*-value = 0.02).

The means of TBOV in patients with positive and negative responses were 13.8 (7.4) and 17.4 (8.8), respectively. The independent t-test has shown that there was no significant difference between groups (*P*-value = 0.055).

The mean of CCCT in group with positive and negative responses were 15.9 (7.4) and 14.7 (4.6), respectively. The independent t-test has shown that there was no significant difference between groups (*P*-value = 0.46).

The mean of AFC in patients with positive and negative responses were 17.8 (7.4) and 22.5 (9.6), respectively. The independent t-test has shown that there was a significant difference between groups (*P*-value = 0.02).

The area under the curve for CCCT, according to a ROC curve analysis to discriminate between ovarian responsiveness and ovarian non-responsiveness, was 0.50, which make this test invalid in prediction of ovarian responsiveness, but if we want to assume a cut-off for this variable according to a receiver-operating characteristic curve, 13.5 with sensitivity and specificity of 52% and 48% respectively can be considered.

Table 1 shows the sensitivity and specificity of each variable in its cutoff. Table 2 shows multiple logistic regression analysis and effect of variables to predict ovarian responsiveness.

Table 1: The sensitivity and specificity of AFC, TBOV, and CCCT in their cutoff points

Variable	Sensitivity (%)	Specificity (%)
AFC	82.6	38
TBOV	56	69
CCCT	52	48

AFC = antral follicles count, TBOV = total basal ovarian volume, CCCT = clomiphene citrate challenge test

Table 2: Multiple logistic regression analysis of variables to predict ovarian responsiveness

Variable	Odds ratio	95% confidence interval	*P* value
AFC	0.935	0.872-0.998	0.04
TBOV	0.98	0.89-1.08	0.34
CCCT	1.04	0.94-1.14	0.48

AFC = antral follicles count, TBOV = total basal ovarian volume, CCCT = clomiphene citrate challenge test

The number of antral follicles was the only significant factor in predicting the ovarian responsiveness.

DISCUSSION

Our data demonstrated that patients with 4-15.5 antral follicles in their ovaries before induction had positive response after induction with clomiphene with sensitivity of 82.6%, and this showed the role of AFC in prediction of ovarian response.

Antral follicle count with transvaginal sonography is a non-invasive and easy to perform method that provides predictive information about ovarian responsiveness before stimulation. The variations in ovarian measurement between ultrasonographer are very small.[6]

The number of small antral follicles in both ovaries assessed by transvaginal sonography was clearly related to reproductive age and could well reflect the size of the remaining primordial follicle pool.[18] In addition, the high intercycle stability of AFC is likely to make this test rather attractive for routine practice;[6] also, it is important to know that for predicting ovarian response and outcome, the AFC measured using techniques based on 3 dimensional ultrasound offers no statistically significant advantage over a measurement, which is limited to information available with conventional 2 dimensional imaging.[19] In recent years, several papers have been published concerning the relation between the antral follicle count (AFC, defined as the total number of antral follicles, sized 2-5 or 2-10 mm, present in both ovaries) and the ovarian response in IVF, as well as the occurrence of the menopausal transition, indicating that this parameter relates strongly to the quantitative aspects of ovarian reserve.[6]

Mean ovarian volume increased from 0.7 cm^3 at age 10 years to 5.8 cm^3 at age 17 years. There are no major changes in ovarian volume during reproductive years until the premenopausal years. Though in menstruating women around age 40, it seems to be a decrease in ovarian size, and this 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 with estrogen treatments, there appeared to be no observed decrease in ovarian volume with age.[20]

Our study showed TBOV had predicting performance in ovarian responsiveness, but is less than AFC. It is demonstrated that patients, who had TBOV within the range of 2.6 15.25 cc before induction, had positive response after induction with clomiphene, with sensitivity of 52%. Although the sensitivity of TBOV in prediction of ovarian responsiveness is less than sensitivity of AFC as transvaginal sonography (TVS) is a reasonably accurate tool for measuring ovarian volume, and its measurement is quick and cost-effective, measurement of TBOV by transvaginal scan before ovulation induction can help in planning the stimulation protocol such as using HMG along with clomiphene citrate[5] and to somewhat prediction of ovarian responsiveness.

CONCLUSION

In our study, we demonstrated that evaluation of CCCT, according to under area in ROC-Curve (50%), cannot contribute in prediction of responsiveness in ovulation induction.

In summary, AFC is a good predictor of ovarian responsiveness. TBOV can predict ovarian responsiveness, but is inferior in comparison with AFC. The CCCT has the least effectiveness.

Therefore, AFC might be considered the test of first choice in the assessment of ovarian reserve before clomiphene induction.

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