Can Doppler Study of the Ovarian Artery Predict the Fertility Outcome of Intrauterine Insemination?

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ABSTRACT: Background. To test the velocimetric pattern of the ovarian artery as a routine ovarian reserve test.

Methods. We enrolled 317 consecutive patients from January 2011 to June 2012. At the second day of the menstrual cycle, a transvaginal ultrasound was performed to evaluate the antral follicle count and ovarian volume, and Doppler of both ovarian arteries was also performed. Controlled ovarian stimulation was performed and the patients were divided in two groups according to the result of the intrauterine insemination: group A (nonpregnant women) and group B (pregnant women).

Results. Ovarian velocimetric pattern was similar between the two groups. Follicle stimulating hormone value had a significant correlation with the ultrasound markers; however, the multiple regression linear analysis showed that the only independent variables were the antral follicle count (t = -2.74, p = 0.008) and the systolic/diastolic ratio (t = 3.95, p = 0.0005). The best parameters in predicting the pregnancy were the mean ovarian volume, total and partial antral follicle count between 7 and 10 mm, and the mean resistance index (area under the curve: 0.744, 0.671, 0.667, 0.573, respectively).

Conclusions. The Doppler study of the ovarian arteries did not add significant information about the ovarian reserve status. Only the mean resistance index had a significant diagnostic accuracy, but its specificity (53%) is too low to consider it a screening test. © 2014 Wiley Periodicals, Inc. J Clin Ultrasound 00:000–000, 2014; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22140

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Assessment of ovarian reserve is a primary step in the study of infertile women. Several markers have been tested over the years. Some may be characterized as passive assessments, as they are simple blood test or ultrasound (US) examinations; others are more provocative, because they rely on the administration of medication followed by recording the stimulatory response. Most ovarian reserve tests have low predictive accuracy in current clinical use; most used blood tests are dosage of follicle stimulating hormone (FSH) and anti-Müllerian hormone, while the most commonly used US test to predict the remaining follicular inheritance is the antral follicle count (AFC). Other parameters such as the mean ovarian volume (MOV) and ovarian vascularity have a low sensitivity, while the study of stromal ovarian artery seems promising. Therefore, we focused on the study of the ovarian artery—and correlated it with other ovarian reserve tests commonly used in clinical practice.

MATERIALS AND METHODS

We conducted a prospective observational study enrolling 317 consecutive patients admitted to
perform intrauterine insemination from January 2011 to June 2012. Inclusion criteria were age between 25 and 42 years, unexplained sterility, bilateral tubal patency, normal spermogram according to World Health Organization 2010 guidelines, regular menstrual cycle (26–30 days), FSH value <20 mIU/ml confirmed on three blood samples, and the presence of both ovaries.

Exclusion criteria were abnormal or frequent anovulatory cycles, polycystic ovaries, history of ovarian surgery, pelvic endometriosis, ovarian cysts, uterine fibromatosis, fluctuating FSH values (markedly different values in the three blood samples), vascular disease such as hypertension, and chronic venous insufficiency. The Local Ethic Committee approved the study. Written informed consent was obtained from all patients.

A complete medical history was obtained and physical examination performed on both partners. Couples were evaluated with hormonal profile at the second day of the menstrual cycle, semen analysis, and tubal patency test. At the second day of the cycle between 8:00 and 9:00 AM, a transvaginal US examination was performed with the patient in the lithotomy position using a PROSOUND 3500 SX scanner and a 5–7-MHz endovaginal probe (Hitachi Aloka Medical, Tokyo, Japan). The length, width, and height of each ovary were measured in the sagittal and coronal planes. Ovarian volume was calculated by using the ellipsoid formula (length × width × height × π/6). The antral follicles less than 10 mm in each ovary were counted and recorded in two categories (AFC2–6 and AFC7–10) according to their size (2–6 mm and 7–10 mm, respectively). MOV (right ovarian volume + left ovarian volume/2) and total AFC (count in left ovary + count in right ovary) were calculated. Using color Doppler, ovarian arterial flow signals were obtained at the hilar region of each ovary. A 2-mm range gate was then placed across the vessel, ensuring that the angle between the Doppler beam and the vessel length was close to 0 degree. A 50–100-Hz filter was used to eliminate low-frequency signals due to the movements of the vessel wall. Pulsatility index, resistance index (RI), and peak systolic flow velocity were calculated electronically from three similar, consecutive waveforms of good quality (Figure 1). The ratio between peak systolic flow and lowest diastolic flow (S/D ratio) was also recorded. All scans were performed by the same operator (E.G.) to avoid interobserver variation. The patients were stimulated with 75 IU of recombinant FSH (Gonal-f; Merck Serono, Darmstadt, Germany) starting from the third day of the menstrual cycle.

The patients were divided into two groups: group A (nonpregnant women) and group B (pregnant women).

All data obtained were recorded and analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL). t test was used for continuous variables and χ2 test for categorical variables. Pearson test was used for assessing the correlations among the ovarian reserve parameters. The receiver operating characteristic (ROC) curve was used to analyze the specificity and sensitivity, and the area under the curve (AUC) was used to represent an overall summary of diagnostic accuracy. A p value <0.05 was considered statistically significant. A confidence interval of 95% was applied where appropriate.

RESULTS

Seventy-seven patients were excluded: 21 for polycystic ovaries, 9 for stimulation cycle suspended, 14 for the suspicion of pelvic endometriosis, 9 for abnormal menstrual cycle, 12 for instable FSH value, 7 for uterine fibromatosis, and 5 for ovarian cyst. Overall, the study population comprised 240 patients whose characteristics were a mean ± SD age of 37 ± 4 years (minimum 29 years, maximum 42 years), a mean ± SD body mass index of 23.3 ± 4.8, mean ± SD FSH value of 7.2 ± 2.6 mIU/ml, a mean ± SD duration of infertility of 2.6 ± 2.1 years, a mean ± SD cycle length of 27.5 ± 2.1 days, and primary and secondary infertility.
rates of 85.4% (205 patients) and 14.6% (35 patients), respectively.

Table 1 shows the baseline characteristics of the patients in the two groups, while Table 2 shows the US findings. When correlating FSH value with the US markers of infertility, we found a significant negative correlation with total AFC ($r = -0.347$, $p = 0.0005$) and AFC$_{7-10}$ ($r = -0.456$, $p = 0.0005$); a significant negative correlation with MOV ($r = -0.359$, $p = 0.0005$), a significant positive correlation with mean S/D ($r = 0.461$, $p = 0.0005$).

However, the multiple regression linear analysis showed that the only independent variables correlated to FSH were AFC$_{7-10}$ ($t = -2.736$, $p = 0.008$) and S/D ($t = 3.952$, $p = 0.0005$).

Considering the correlation of the spectral Doppler indices with the other US parameters, we found a significant positive correlation between mean pulsatility index and AFC$_{2-6}$ ($r = 0.343$, $p = 0.0005$); a significant negative correlation between mean S/D and MOV ($r = -0.427$, $p = 0.0005$); a significant positive correlation between mean peak systolic flow velocity and AFC$_{2-6}$, total AFC, and MOV ($r = 0.444$, $p = 0.0005$; $r = 0.368$, $p = 0.0005$; $r = 0.433$, $p = 0.0005$, respectively).

The ROC curves showed that the best parameters in predicting the pregnancy were MOV, total AFC, AFC$_{7-10}$, and mean RI (with area under the curves of 0.744, 0.671, 0.667, 0.573, respectively; Figure 2). The best threshold values were 4.3 cm$^2$ for MOV (sensitivity 83%, specificity 49%), 11 for total AFC (sensitivity 77%, specificity 57%), 6.5 for AFC$_{7-10}$ (sensitivity 66%, specificity 65%), and 0.87 for mean RI (sensitivity 77%, specificity 53%).

**DISCUSSION**

Currently, there is no uniformly accepted definition of decreased ovarian reserve. Several tests have become part of the standard pretreatment
assessment for in vitro fertilization (IVF) designed to predict oocyte yield and pregnancy rate. One of the most studied tests is the early follicular phase FSH level, whose increase is a direct pituitary compensation for the older and less responsive ovary. A threshold FSH value is not uniformly accepted. Women with a FSH <15 mIU/ml are twice as likely to conceive as women with FSH between 15 and 24.9 mIU/ml. This finding was consistent with another series reporting a significant decline in conceptions when FSH exceeded 20 mIU/ml. However, a recent meta-analysis showed that the role of FSH testing is best limited to screening and patient counseling purposes. Another important serum test whose clinical performance has not been definitely established is the dosage of anti-Müllerian hormone. US is taking an increasingly important role in the field of infertility. For instance, AFC has been considered the first-line test for ovarian reserve by some authors. However, the accuracy of this test in predicting poor responses seems to be satisfactory only at a low threshold level so that other authors are questioning its clinical value to predict pregnancy. The use of MOV has been much debated and MOV has been reported as an important predictor of reproductive success, superior to FSH or estradiol concentrations. However, when used alone, this measurement does not seem to be accurate in predicting non-pregnancy in IVF patients. Transvaginal duplex US has been used quite extensively to assess ovarian blood flow patterns in both natural and stimulated cycles. Recent studies found a significant positive correlation between a high ovarian perifollicular blood flow in the early follicular phase of IVF and a high clinical pregnancy rate. Some researchers found that periovulatory subfollicular vascularization index and vascularization flow index were lower in women undergoing intrauterine insemination who became pregnant, suggesting their use as markers of follicular quality and pregnancy predictors. Other authors found a correlation between early follicular stromal Doppler signals and ovarian response as well as basal ovarian reserve parameters, but no correlation with clinical pregnancy achievement in infertile women undergoing IVF treatment. However, a meta-analysis for predictive capacity of ovarian vascularity cannot be completed due to the heterogeneity of the studies.

Considering the promising results of the use on the ovarian vascularization index, we wanted to test the reliability of the velocimetric pattern of the ovarian artery as follicular reserve test. The main outcome was the onset of pregnancy, which defined the two groups of women. The baseline characteristics of the couples were fairly homogeneous with only age and FSH value being different between the two groups. This is an expected result because the importance of the age and FSH factors on assisted reproductive techniques is well known. The comparison of the US parameters showed a significant difference for MOV, total AFC, and AFC$_{7-10}$, whose values were higher in the group of pregnant women, thus confirming the results of previous studies. Pearson’s test and multiple linear regression analysis confirmed the reliability of these parameters, which correlated significantly with FSH values.

ROC curves confirmed previous observations, in demonstrating the reliability of the MOV, AFC, and AFC$_{7-10}$ in predicting pregnancy with a diagnostic accuracy of 74%, 67%, and 66%, respectively, whereas among the ovarian velocimetric indices the only mean ovarian RI had a good sensitivity (77%) but a low specificity (53%).

Our study confirms findings previously reported in the literature. FSH is a good screening tool but it is not a diagnostic test to predict pregnancy. Grayscale US measurements, when used together, are useful in the evaluation of the infertile patient but have a poor individual diagnostic accuracy.

Unfortunately, Doppler study of the ovarian arteries did not yield useful results regarding the ovarian reserve status. Currently, the Doppler study of ovarian arteries cannot be considered as a marker of fertility outcome.
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