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Original Article

Assessment of ovarian reserve in infertility

Agarwal Mukta [1], Das Vinita [2], Agarwal Anjoo [3], Pandey Amita [4], Natu SM [5]

[1] Junior Resident-III, [2] Professor and Head, [3] Associate Professor, [4]Assistant Professor, [5] Professor

Department of Obstetrics and Gynaecology, CSM Medical University, Lucknow.

Abstract

Objectives: To evaluate various clinical, laboratory and radiological tests of ovarian reserve available for prediction of successful ovulation induction in infertility. *Methods :* The study comprised of 54 infertile women, who underwent evaluation of various clinical, biochemical and sonological parameters for the assessment of ovarian reserve i.e. measurement of day-3 serum FSH levels, clomiphene citrate challenge test (CCCT) and number of antral follicles. Outcome variables were S. estradiol levels and endometrial thickness at the time of ovulation trigger, presence of ovulation, S. progesterone levels 7 days after ovulation trigger and pregnancy rate. *Results:* Among the various tests used CCCT was found to be a better predictor of ovarian reserve. There was statistically significant decrease in the levels of S. estradiol, S. progesterone and endometrial thickness in patients with abnormal CCCT. No pregnancy occurred in cases with abnormal CCCT. *Conclusion:* CCCT was found to be better than D-3 FSH or number of antral follicles to predict ovarian reserve. Assessment of ovarian reserve is important for prediction of outcome prognosis of ovulation induction as diminished ovarian reserve is associated with suboptimal response to ovulation induction.

Key words: ovarian reserve, FSH levels, clomiphene citrate challenge test (CCCT), antral follicle count

Introduction

In today's world, medical science has various new and advanced technologies like ART and IVF to help those numerous childless couples, who are seeking treatment for infertility but it would be nice if we had some test to provide the outcome prognosis for assisted reproductive technology. In this context the concept of ovarian reserve is very important which refers to the size of resting primordial follicles that presumably determines the number of growing follicle population and quality and reproductive potential of their oocytes. Therefore ovarian reserve is thought to affect how ovaries respond to pharmacological doses of exogenous gonadotropins. This oocyte related decline in fertility is known as decreased ovarian reserve. In clinical practice, diminished ovarian reserve is found to be associated with suboptimal response to ovulation induction, decreased pregnancy rates after ART, and increased risk of miscarriage and fetal aneuploidy.

Various tests used for the prediction of ovarian reserve are measurement of serum FSH levels on the third day of menstrual cycle, clomiphene citrate challenge test (CCCT) and antral follicle count.

However, many controversies exist regarding the best

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Correspondence :
Dr. Das Vinita
B-2, Sector -B, Aliganj,
Lucknow (U.P.) 226024 India
Mobile - 09839009980 Email : das_lko@yahoo.com

test for measurement of ovarian reserve. So, the present study was conducted to assess the predictive value of various tests available for evaluating ovarian reserve and to know the most valuable test out of those.

Material and methods

This study was a prospective clinical trial conducted in the infertility unit of the Department of Obstetrics & Gynaecology in collaboration with Department of Pathology of a tertiary care teaching hospital of North India. The study included 54 women registered in the infertility unit and planned for ovulation induction and intrauterine insemination.

The patients with male factor infertility, infertility due to tubal factors, irregular or undiagnosed vaginal bleeding, ovarian cysts, documented ovarian failure and history of ovarian neoplasm were excluded from the study.

In the present study, we used the following clinical, biochemical and radiological tests for the assessment of ovarian reserve and thereby prediction of successful outcome of ovulation induction amongst our registered patients.

On the day of registration, explained and informed consent was obtained and the following clinical parameters were noted - age, weight, body mass index, parity, age at menarche, length of menstrual cycle, mother's age at menopause and presence of gray hair in the patient. On the third day of menstrual cycle, serum FSH levels were estimated and baseline ultrasonography was done at which the antral follicle count was noted.

All the patients underwent CCCT, which incorporates D-3 (3^{rd} day of menstrual cycle) FSH levels followed by tablet clomiphene citrate 100 mg orally once a day for five days and repeat S-FSH on D-10 (10^{th} day of menstrual cycle) of cycle (value $\geq$10 mIU/ml on either day of the cycle indicates abnormal test).

From day 7 onwards, USG was done on alternate days for size and number of follicles and endometrial thickness. When follicle size was $\geq$16 mm, endometrial thickness and S. estradiol levels were measured and injection HCG 5,000 IU intramuscular was given for triggering ovulation.

Ultrasonography was done daily thereafter to detect ovulation and intrauterine insemination was done in all the patients fro two consecutive days 24 and 48 hours after the injection HCG. Seven days after giving injection HCG, S. progesterone levels were measured. In luteal phase, all patients received 100mg micronized progesterone twice daily, vaginally. All the patients were followed for pregnancy.

Chi Square and Fischer's exact test (as indicated) were used for statistical analysis.

Results

Fifty four subjects were included in the study. Among the clinical parameters under study, only subject's age (p=0.048) was found to be having significant negative correlation with prediction of pregnancy (Table 1).

Table 1. Pregnancy outcome in relation to clinical characteristics.

Clinical characteristics		Pregnancy outcome (n=54)		
		Pregnancy present (n=4)	Pregnancy absent (n=50)	p-value
1. Age		25.5 ± 2.38	30.13 ± 4.5	0.048 (S)
2. BMI		21.24 ± 0.8	21.23 ± 3.2	0.99
3. Presence of grey hair (n=31)*		1/31 (4%)	30/31 (96%)	0.202
4. History of mother's age at menopause (n=54)	<40 yrs (n=5)	0/0 (0%)	5/5 (100%)	0.67
	>40 yrs (n=49)	4/49 (8%)	45/49 (92%)	

Chi-square test
*Fisher's exact test

Table 2. Pregnancy outcome in relation to various tests used to predict ovarian reserve.

Test of ovarian reserve		Pregnancy outcome (n=54)		
		Pregnancy present (n=4)	Pregnancy absent (n=50	p-value
1. D-3FSH	4.67 ± 1.99	6.52 ± 3.41	0.87	
2. No. of AF*	≤3 (n=21)	1 (25%)	20 (40%)	0.492
	>3 (n=33)	3 (75%)	30 (60%)	
3. CCCT*	Normal (n=47)	4 (100%)	43 (86%)	0.564
	Abnormal (n=7)	0 (0.0%)	7 (14%)	

(Normal CCCT – Day 3 and Day 10 FSH <10 mIU/ml Abnormal CCCT – Day 3 and/or Day 10 FSH ≥10 mIU/ml)
Student's 't' test *Fisher exact test

Table 3. Evaluation of other outcome variables in relation to CCCT.

Variable	Normal CCCT (n=47)	Abnormal CCCT (n=7)	p-value
*Peak S. Estradiol (pg/ml)	207.5 ± 171.1	74.54 ± 44.98	0.001 (S)
* Serum progesterone (ng/ml)	67.09 ± 69.24	17.6 ± 23.12	0.01 (S)
Endometrial thickness (cm)	1.07 ± 0.2	0.91 ± 0.05	0.04 (S)
Ovulation occurred **	46	5	0.04 (S)

*Principle of outlayering was used during statistical analysis.
** Fisher exact test

Table 4. Correlation of various clinical parameters under study with CCCT.

S.No.	Clinical parameter		Normal CCCT (n=47)	Abnormal CCCT (n=7)	p-value
1.	Age		30.50 ± 3.27	31.24 ± 2.25	0.12
2.	Body mass index		20.12 ± 2.95	21.2 ± 2.50	0.24
3.	Recurrent pregnancy loss (n=3)*		1 (2.13%)	2 (28.57%)	0.041 (S)
4.	Mother's age at menopause*	<40 years (n=5)	4 (8.51%)	1 (14.29%)	0.515
		>40 years (n=49)	43 (91.49%)	6 (85.71%)	
5.	Presence of grey hair (n=31)		27 (57.45%)	4 (57.14%)	0.606

Student's 't' test; chi-square test; *Fisher exact test

Day 3 FSH and antral follicle count were not found to be significantly correlated with the prediction of pregnancy, statistically. Correlation of CCCT and pregnancy outcome was also not found to be statistically significant, which may be due to the small size of the sample. However it is important to note that no pregnancy occurred in patients with abnormal CCCT (Table 2).

Among the other outcome variables besides pregnancy, peak serum estradiol level (p=001), serum progesterone level (p=0.01), endometrial thickness (p=0.004) and anovulation (p=0.04) were significantly lower in patients with abnormal CCCT (Table 3). Besides this incidence of recurrent pregnancy loss was higher in abnormal CCCT group (p=0.041) (Table 4).

Discussion

Unlike the male, a female is born with a finite number of eggs, which are not only lost by ovulation but also there is a natural loss – whereby eggs are dying every day. Therefore an assessment of the ovarian reserve is important and should be one of the foremost steps in the workup of an infertile couple, as it gives a realistic estimate to the couple of the likelihood of conception with treatment.

An optimal test for assessing ovarian reserve may be an index that incorporates several serum markers and clinical and radiological data. However, CCCT stands out to be a better test among all the tests available. Rationale behind this test is that as the follicle develops, patients with normal ovarian function will produce levels of inhibin and estradiol sufficient to suppress FSH production by the tenth day of menstrual cycle.

In our study, we found no pregnancy, more incidence of anovulation and significant lower peak Serum estradiol and D_{21} S. progesterone in the group of subjects having abnormal CCCT. Tobar Hicks et al[1] found significant correlation of abnormal CCCT with patients age, BMI, mother's age at menopause and cycle interval. In our study we found abnormal CCCT to be correlated with only one clinical parameter i.e. recurrent pregnancy loss. There was no significant association with age. Magendzo et al[2] reported that pregnancy rates are significantly lower in patients with abnormal CCCT (25% vs. 46.7%, p<0.02). Csemiczky[3] also found CCCT to be a useful tool in assessing a woman's ovarian capacity before infertility treatment. Scott[4] after reviewing literature found that the screening tests are valuable in assessing ovarian reserve. On the contrary, Brockman et al[5] concluded that the use of any ovarian reserve test for outcome prediction cannot be supported.

Conclusion

Assessment of the ovarian reserve is important for prediction of outcome of ovulation induction as diminished ovarian reserve is associated with suboptimal response to ovulation induction.

Our study shows that age of the patient and CCCT should be included in work up of every case of infertility in order to assess the ovarian reserve, especially as these are simple tests available universally. But larger studies are required to further evaluate the usefulness of these tests. Studies are also required to evaluate some of the newer tests like inhibin B[6], anti-mullerian hormone[7] and granulose cell telomerase activity which also have the limitation of being expensive and available only in selected centers.

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Reference

1. Tobar Hicks AB, Fox MD, Sanchez-Ramos L et al. Clinical characteristics of patients with an abnormal clomiphene citrate challenge test. Am J Obstet Gynecol 2003;189:348-52.
2. Magendzo A, Schwarze JE, Diaz de la Vega C et al. Clomiphene citrate challenge test predicts outcome of intrauterine insemination in women aged under 37 years. Reprod Biomed Online 2006;12:423-7.
3. Csemiczky G, Harlin J, Fried G. Predictive power of clomiphene citrate challenge test for failure of in vitro fertilization treatment. Acta Obstet Gynecol Scand 2002;81:954-61.
4. Scott RT Jr., Hofmann GE. Prognostic assessment of ovarian reserve. Fertil Steril 1995;63:1-11.
5. Broekmans FJ, Kwee J, Hendriks DJ et al. A systematic review of tests predicting ovarian reserve and IVF outcome. Human Reprod Update 2006;12:685-718.
6. Halder A, Fauzdar A, Ghosh M et al. Serum inhibin B: A direct and precise marker of ovarian function. J Clin Diagn Res 2007;24:131-7.
7. Tremellen KP, Kolo M, Gilmore A et al. Anti mullerian hormone as a marker of ovarian reserve. Aust N Z J Obstet Gynaecol 2005;45:20-4.