

An evaluation and comparison study of ovarian reserve in fertile and infertile south Indian women population

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Abstract

Infertility accounts to nearly one-third of the patients who seek the medical advice of a gynecologist. Infertility or otherwise sub fertility is the failure of a couple to conceive after 1 year of regular, unprotected intercourse. Amongst the various causes for female infertility ovulatory dysfunction is the most common and accounts to 30-40% of all cases.¹ The capacity of an ovary to produce egg cells that are capable for fertilization is known as ovarian reserve. Tests done to assess quantitative ovarian reserve of a woman desirous of pregnancy includes Day 3 FSH, AMH, Antral follicular count and ovarian volume measurement. Antral follicular count is referred as a number of oocytes and follicles in ovaries which is morphologically healthy. Anti mullerian hormone is produced by healthy ovarian follicles and serves as a marker of quantity of healthy follicles and oocytes in ovaries. Ovarian volume assessed by ultrasound can be used as a marker of functional ovarian potential. The aim of this study is to compare the ovarian reserve of fertility proven women with women presenting with sub-fertility using the sonographic tests like antral follicular count and ovarian volume measurement in a tertiary care teaching hospital in Thoothukudi, Tamil Nadu, South India and thence to assess if they are corresponding to standard cut-off values of other parts of the globe.

Keywords: Ovarian reserve, Antral follicular count.

Review of Literature

Ovarian Reserve: The reproductive potential of a woman is determined by her capacity to produce healthy functional oocytes in every menstrual cycle. Ovarian reserve is the size and number of resting or non-growing primordial follicles and its evaluation is a useful predictor of the possible number of oocytes that would be available during that cycle. It is best evaluated on Day 2 of a cycle enabling the physician to decide regarding the use of exogenous hormones for stimulation of the ovary for an ART procedure. Judicious use of exogenous hormones is recommended as there is a risk of failure to ovulate if the reserve seems to be insufficient and also the risk of life threatening hyper-stimulation syndrome if the number of immature follicles are plenty. Age of the woman seeking fertility treatment is also a major determining factor of success as increasing age is associated with diminishing ovarian reserve. An increasing age is inversely proportional to the release of healthy functional eggs and thus can affect the success of the procedure done.

Screening Tests for Ovarian Reserve

Measurement of Day 3 FSH: FSH is a pituitary hormone that helps in promoting follicular growth and maturity. Its release is affected by a positive feedback from the hypothalamic hormone and a negative feedback by the ovarian hormones. Evaluation of Day 3 FSH helps in predicting the extent of negative feedback offered by the ovarian hormones thus indirectly

assesses the functional capacity of an ovary. A value more 12mIU/ml carries lesser chance of success in ART. If more than 25mIU/ml confirms with menopausal level denoting ovarian failure due to decreased ovarian reserve and it is advisable to offer egg donation as an option for pregnancy.

Basal Estradiol Level: Growing follicles produce estrogen and basal estradiol level done of Day 3 helps to estimate the functional capacity of the growing follicles.

Serum Inhibin B: Inhibin B is secreted by ovarian granulosa cells from the pre-antral follicle stage and reflects the overall granulosa cell function of the group of follicles that are recruited to undergo gonadotropin-dependent growth. The patients with Inhibin B levels of less than 400 pg/ml have a significantly less number of follicles.

Serum Antimullerian Hormone (AMH): The granulosa cells of both pre-antral and small antral follicles produce AMH. It can be measured during any phase of the menstrual cycle. Its function is to inhibit the initiation of growth of the primordial follicle. In women with regular cycle, the serum level of AMH declines with age and it becomes undetectable by menopause. AMH can be used as a marker for depletion of ovarian reserve as a decreasing level indicates that there is a decrease in primordial follicle count. Decreased levels of AMH in the early follicular phase correspond to poor ovarian reserve in ART cycles.

Normal AMH-1.5-4.0

Low AMH-0.5-1

High AMH>4

Antral Follicular Count: The antrum of ovary is the site for presence of developing follicles that would respond to stimulation with exogenous hormones. A Transvaginal ultrasound evaluation of antral follicular count on Day 2 or 3 helps to predict the possible number of ova that may be released if the ovary is put under the effect of stimulation drugs. All ovarian follicles measuring between 2-10 mm in both ovaries are counted and the total value obtained is called basal antral follicle count (AFC). It is suggested that counting all antral follicles of size 2-10mm in diameter is the preferable method. Three dimensional automated follicular tracking is a newer advanced technique that helps to eliminate inter and intra observer variations.

Ovarian Volume: The human ovary is an organ which changes in size and activity throughout life. At birth, the ovary is ~1cm in length and weighs <0.3g. The ovary decreases slightly in volume at 1 month of age, probably due to the clearance of maternal estrogen from the female neonate (Haber and Mayer 1994). Ivarson *et al* in 1983 demonstrated that there was an increase in mean volume of ovary from 0.7cm³ to 5.8cm³ through 10 years to 17 years of age. Adult ovaries are ovoid, measure approximately 3-5cm by 1.5-3cm by 0.6-1.5cm and weigh 5-8g. Following menopause, the ovaries will shrink to about one-half of their size as seen in the reproductive period. Tepper *et al* found a linear relationship between menopause age and ovarian volume. The mean ovarian volume dropped from 8.6cm³ a year after the menopause to 2.2cm³ 15 years into menopause.

Measurement of Ovarian Volume by Transvaginal Ultrasound: Women having a mean ovarian volume of <3cm³ have a higher chance of follicular stimulation failure.³⁷ The size of ovaries is essential in the diagnosis of OHSS and is useful for grading the severity of it. The ovaries are measured in three planes and the ovarian volume was calculated using the ellipsoid formula $V=D1 \times D2 \times D3 \times 0.523$.

D1, D2, D3 are the three maximal longitudinal antero-posterior and transverse diameters respectively. Three dimensional Transvaginal ultrasound is now proving to be useful to predict ovarian responsiveness to ovulation induction drugs.

Aim of the Study

1. To establish the role of AFC as a function of ovarian reserve in fertility-proven and in sub fertile Indian women.
2. To know the cut-off value of antral follicle count in normal and infertile women in South Indian population.
3. To assess if there is a difference in the ovarian volume between fertile and infertile women in South Indian population

Settings and Design: Case-control study done at Govt. Thoothukudi Medical College Hospital, Thoothukudi a

tertiary care teaching hospital in Tamil Nadu, South India.

Inclusion Criteria

For Cases:

1. Primary infertility
2. No ovarian abnormality (polycystic ovary, ovarian endometriomas) as assessed by transvaginal USG.
3. No evidence of uterine malformations or uterine pathology.
4. No evidence of endocrinal disease
5. No evidence of previous ovarian surgery

For Controls

1. Proven natural fertility by having at least one pregnancy carried to term
2. Regular menstrual cycles,
3. No evidence of endocrinal disease
4. No history of ovarian surgery

Exclusion Criteria

1. H/O ovarian abnormality like polycystic ovary, ovarian endometriomas
2. History and any evidence of uterine malformations or uterine pathology,
3. H/o endocrinal disease
4. H/o previous ovarian surgery
5. Hormonal contraception stopped > 3 months before entering the study protocol.

Sample Size: Sample size for frequency in a population – 50 cases and 50 controls.

Study Method: The basal ovarian volume and AFC were measured by endovaginal ultrasound on the second or third day of the menstrual cycle. The measurements were done by the same observer for all patients to avoid bias.

1. All follicles 2-10 mm size range of well-defined anechoic cysts with smooth margins and absence of internal septations or nodularity were measured and counted in each ovary. The sum of follicular count in both ovaries was labeled as Antral follicular count.
2. The ovaries were measured in three planes and the ovarian volume was calculated using the prolate ellipsoid formula $V=D1 \times D2 \times D3 \times 0.523$. D1, D2, D3 are the three maximal longitudinal antero-posterior and transverse diameters.

The results were analysed after being grouped as follows:

Age

Age Group 1 25– 30yrs

Age Group 2 31 -35 yrs

Among infertile group 25 in group 1, 25 in group 2

Among fertility proven control group 26 in group 1, 24 in group 2

The mean standard deviation of the both infertile and control group showed that there exists a statistical significance among the two groups with response to age.

Ovarian VolumeGroup 1 – 9-11cm³Group 2 - ≥11 cm³

Among infertile group 25 in group 1, 25 in group 2

Among control group 21 in group 1, 29 in group 2

Table 1

Group statistics group	n	Mean	Standard deviation	Standard error mean	Significance P
Ovarian volume 1 (infertile)	50	10.86	1.639	0.299	0.184
0 (control)	50	11.36	1.211	0.221	0.185

The mean standard deviation of the both infertile and control groups that was found revealed that there is no statistical significance among the two groups with regard to ovarian volume.

Antral Follicular Count

Group 1 – Count >8 follicles

Group 2- Count ≤8 follicles

Among infertile group 16 in group 1, 34 in group 2

Among control group 40 in group 1, 10 in group 2

Table 2

Group statistics	n	Mean	Standard deviation	Standard error mean	Significance P
1 (infertile)	50	6.67	1.688	0.308	0.000
2 (control)	30	11.23	2.112	0.386	0.000

The mean standard deviation of the both infertile and control group revealed that there exists a statistical significance among the two groups with response to antral follicular count.

Result

On comparative analysis of biophysical and sonographic variables in infertile and fertile patients, the given table shows that there is no change in ovarian volume in both the cases and the controls but there is significant change in antral follicular count in both groups when a cutoff of 8 was used.

Table 3

Variables	Cases (n=50) (Mean±SD)	Controls (n=50) (Mean±SD)	P Value
AGE(years)	31.30±2.466	29.80±2.355	0.0134
BMI(kg/m ²)	22.70±2.672	22.22±2.194	0.4568
Antral follicle count(AFC)	6.67±1.688	11.23±2.112	0.0001
Total ovarian volume(cc)	10.86±1.639	11.36±2.112	0.4113

Discussion

The study showed there is a difference in antral follicular count that was statistically significant between the fertile and the infertile women. The follicular count was lower in infertile women when compared to fertile women of especially of age group 25-35 years (P<0.001). There was also a difference of the cut-off values between Western women and in our South Indian women; the study demonstrated that the AFC of even fertility proven South Indian women was lower than those of their western counterparts. This variability in the value of AFC is most probably due to the differences in the race, socio-economic and geographic background of Indian and western populations. A cut off value of 8– at least 4 in each ovary may be used to signify chances of success in patients undergoing assessment for female factor infertility. The results of this study substantiates the fact

that AFC can be used as a valuable predictor of fecundity in South Indian women of child bearing age in terms of capability to conceive on a two point scale (i.e. positive or negative). Also noted in our study was that there was no statistically significant evidence to show that the ovarian volume was different in the fertility proven and sub-fertile women.

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