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Prediction of ovarian reserve in sub-fertility: A comparative study

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Abstract
Introduction: Infertility is the failure of a couple to conceive after 1 year of regular, unprotected intercourse. Ovulatory disorder is one of the most common reasons of female factor infertility 30% of all cases). The term denotes the capacity of the ovary to provide egg cells which is capable for fertilization results in a good outcome which in turn means a successful pregnancy. With advanced maternal age the capability of the ovary to produce egg cells will decline, constituting a major factor in the inverse correlation between age and female fertility. However, between women of the same chronological age, the quantitative ovarian reserve may vary substantially. To assess the individual quantitative ovarian reserve[90], various ovarian reserve tests (ORTs) have been developed, viz. (1) day□3 follicle stimulating hormone (FSH), (2) anti□Mullerian hormone (AMH) and (3) antral follicle count (AFC).
Aim: (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.
Methodology: All the patients attending gynecology outpatient department in reproductive age group (25-35yrs) who are all undergoing workup for infertility are included -50 cases. They were all compared to equal number of controls (fertility proven) in same age group (25-35yrs). 50 controls.
Period: January 2018 to June 2018.
Place: Department of OG, Govt. KMC Hospital.
Results: On evaluating antral follicles up to 10mm in diameter, significant difference in numbers was noted in my study population (6.698± 1.688 in cases; 11.46 ± 2.169 in controls; p value of <0.0001). A cut off value of >9 follicles (Aggregate of both ovaries) may be taken as a standard for successful pregnancy outcome.
Conclusion: The results of this study indicate that AFC is a viable 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). The mean AFC in South Indian women is significantly different from that noted in Western literature, mainly due to racial, geographic and socio-economic reasons. A cut off value of >9 may be used to prognosticate patients undergoing assessment for female factor infertility. On the other hand same data can be utilized for optimum patient selection for ART. This would in turn lead to a higher success rate of this technique.

Keywords: AFC, ART and sub fertile

Introduction

Infertility

Infertility is the failure of a couple to conceive after 1 year of regular, unprotected intercourse. Ovulatory disorder is one of the most common reasons of female factor infertility 30% of all cases) [1].

Ovarian Reserve

The term denotes the capacity of the ovary to provide egg cells which is capable for fertilization results in a good outcome which in turn means a successful pregnancy. With advanced maternal age the capability of the ovary to produce egg cells will decline, constituting a major factor in the inverse correlation between age and female fertility. However, between women of the same chronological age, the quantitative ovarian reserve may vary substantially. To assess the individual quantitative ovarian reserve[90], various ovarian reserve tests (ORTs) have been developed, viz. (1) day□3 follicle stimulating hormone (FSH), (2) anti□Mullerian hormone (AMH) and (3) antral follicle count (AFC).

Antral follicle count

Antral follicular count is referred as a number of oocytes and follicles in ovaries which is morphologically healthy and associated with serum concentrations of anti-mullerian hormone. Anti mullerian hormone is a marker of quantity of healthy follicles and oocytes in ovaries. Antral follicular count measured by serial transvaginal ultrasonography during follicular phase is reproducible within an individual.

Ovarian volume

Ovarian volume is an important tool in the screening, diagnosis and monitoring the treatment of conditions such as polycystic ovarian syndrome, ovarian cancer and adolescent abnormalities in reproductive medicine. Recent advances in technology, including the trans vaginal scan have made possible the measurement of ovarian volume both easy and cost effective. Measurement of ovarian volume has a role in the assessment of ovarian reserve and prediction of response to superovulation.

Reproductive aging is considered to be the consequence of a decrease in the quantity and quality of the ovarian follicle pool. [1□3] Autopsy studies of human ovaries show that the number of follicles decreases rapidly with female age, starting in fetal life and continuing until after menopause. The number of antral follicles and the total ovarian volume as measured by transvaginal USG have been mentioned in the literature to predict declining fertility related to reproductive aging. [4□7] Studies concerning physiological ovarian aging in women with and without fertility problems are very limited and most of them are done in Western countries. It, therefore, seems warranted to evaluate the aforementioned Sonographic test parameters in women of different ages in India.

Assisted reproductive technologies

Assisted reproductive technology include In vitro fertilisation, Intra cytoplasmic sperm injection, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), cryopreserved embryo transfers and the use donor oocytes**.** The performance of ZIFT and GIFT has declined now days because of the increased success rate of IVF and ICSI [1].

Both involves the following processes

- premature LH surge prevention
- Monitoring of follicular growth
- Pretreatment
- Adjunctive medications
- Triggering of ovulation and oocyte maturation
- Retrieval of oocytes
- Luteal support
- Fertilization either by IVF or ICSI
- In vitro embryo culture
- Transfer of fresh embryo
- Cryopreservation of other surplus embryo
- Monitoring of pregnancy during first trimester

Complications

- Cycle cancellation -6%
- Risks of oocyte retrieval include bleeding requiring transfusion, injury to adjacent structures requiring laparotomy, pelvic abscess formation leading to loss of reproductive function
- Multiple gestation
- Ectopic and heterotopic pregnancy
- Ovarian hyperstimulation syndrome
- Risk of cancer after fertility therapy
- stress

Aims

(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.

Materials and Methods

Case - control study. Place of the study: Dept. of OBGYN, Govt. KMC.

Period: January 2018 to June 2018.

Trans vaginal ultrasound

Inclusion Criteria

Cases

(i) Primary infertility
(ii) No ovarian abnormality (polycystic ovary, ovarian endo-metriomas) as assessed by transvaginal USG.
(iii) No evidence of uterine malformations or uterine pathology,
(iv) No evidence of endocrinological disease
(v) No evidence of previous ovarian surgery

Controls

(i) Proven natural fertility by having at least one pregnancy carried to term
(ii) Regular menstrual cycles,
(iii) No evidence of endocrinological disease,
(iv) No evidence of ovarian surgery,
(v) No ovarian abnormality as assessed by transvaginal USG, and

Exclusion Criteria

I) Any H/O ovarian abnormality like polycystic ovary, ovarian endometriomas
II) History and any evidence of uterine malformations or uterine pathology,
III) H/o endocrinological disease, and
IV) H/o previous ovarian surgery
V) Hormonal contraception stopped > 3 months before entering the study protocol.

Sample Size

Sample size for frequency in a population – 30 cases and 30 controls

Sampling Methods

- All the patients attending gynecology outpatient department in reproductive age group (25-35yrs) who are all undergoing workup for infertility are included
- They were all compared to equal number of controls (fertility proven) in same age group (25-35yrs).
- The basal ovarian volume and AFC were measured by endovaginal ultrasound.
- Transvaginal USG was carried out on the second or third day of the menstrual cycle.
- Thorough survey of each ovary was done by scanning from the outer to the inner margin.
- All follicles having adequate morphology as described for a healthy follicle (i.e., 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.
- The ovaries are measured in three planes and the ovarian

volume was calculated using the prolate ellipsoid formula V=D1xD2xD3x0.523. D1, D2, D3 are the three maximal longitudinal antero-posterior and transverse diameters respectively.

Results: Age group *GROUP

Table 1: Age group with Fertility Proven and subfertile group.

Crosstab					
			Group		
			Fertility proven	**Sub fertile**	**Total**
Age group	25-30	**Count**	32	30	62
		% within GROUP	64.0%	60.0%	62.0%
	31-35	Count	18	20	38
		% within GROUP	36.0%	40.0%	38.0%
	Total	Count	50	50	100
		% within GROUP	100.0%	100.0%	100.0%

Chi square = 0.170 P = 0.680 Not Significant. There is no statistical significance between two groups with respect to different age group.

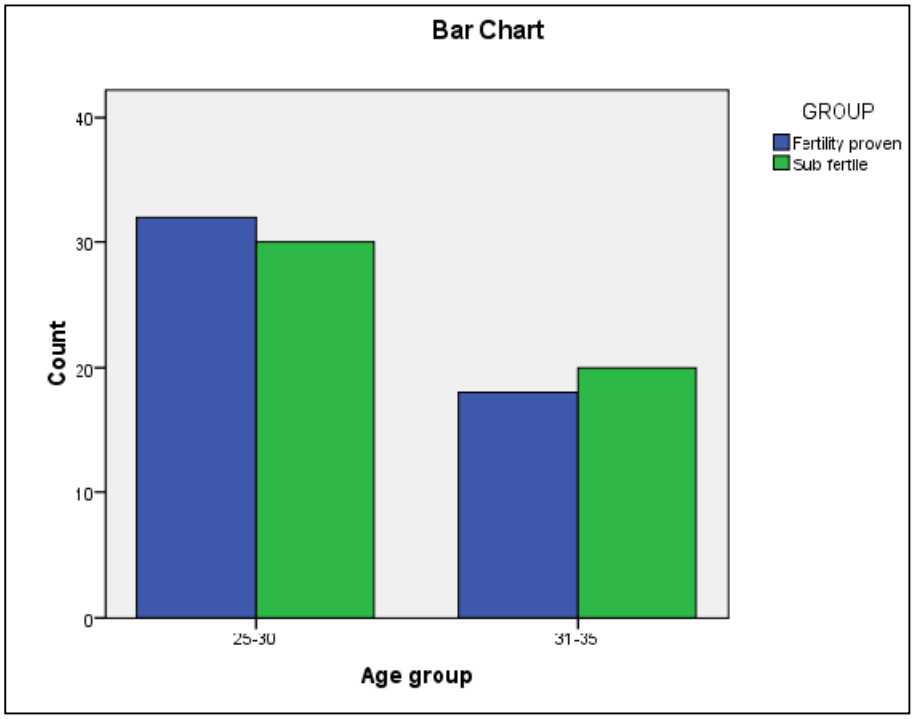

Fig 1: Age Group Distribution

Table 2: Biomarkers of AFC and Ovarian Volume with Study and Control Group.

Group Statistics						
	GROUP	N	Mean	Std. Deviation	Std. Error Mean	P
AFC	Sub fertile	50	6.98	1.610	.228	0.000
	Fertility proven	50	11.46	2.169	.307	SIGNIFICANT
OVARIAN VOLUME	Sub fertile	50	10.9914	1.58306	.22388	0.237
	Fertility proven	50	11.3296	1.23775	.17504	NOT SIGNIFICANT

From above we infer the mean level of AFC is 6.98 for sub fertile women and 11.46 for fertility proven women. This is statistically significant.

In ovarian volume the mean level is 10.99 for sub fertile women and 11.32 for fertility proven women. The difference mean is not that much high and they are not statistically significant.

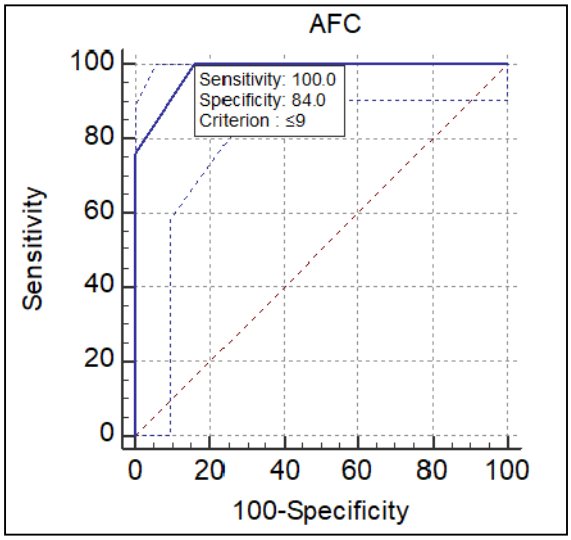

Fig 2: Receiving operating curve for AFC

ROC curve

Variable	AFC
Classification variable	Group
Sample size	100
Positive group: Group - 1	50
Negative group: Group – 2	50
Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.981
Standard Error[a]	0.00796
95% Confidence interval[b]	0.931 to 0.998
z statistic	60.421
Significance level P (Area=0.5)	<0.0001

The Receiving Operating curve for AFC between sub fertile and Fertility proven women with a Area under curve =0.981, clearly indicates AFC is a very good predictor for sub fertile women.

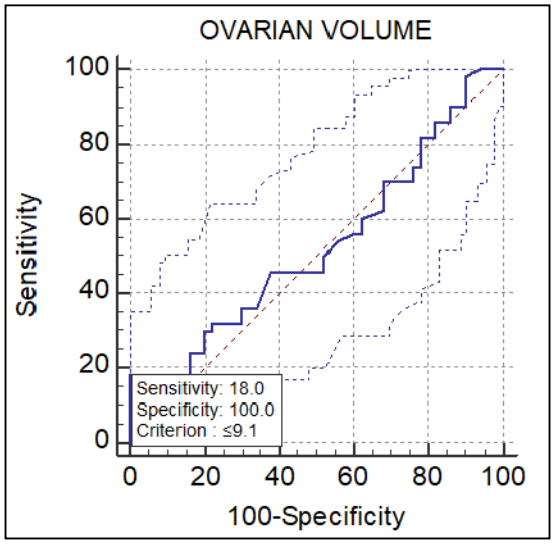

Fig 3: Receiving operating curve for ovarian volume

ROC curve

Variable	Ovarian Volume
Classification variable	Group
Sample size	100
Positive group: Group = 1	50
Negative group: Group = 0	50
Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.529
Standard Error[a]	0.0586
95% Confidence interval[b]	0.427 to 0.630
z statistic	0.501
Significance level P (Area=0.5)	0.6161

The Receiving Operating curve for Ovaroam volume between sub fertile and Fertility proven women with a Area under curve = 0.529, clearly indicates Ovarian volume is not a good predictor for sub fertile women.

Discussion

Limited data is available on ovarian ageing in the sub-fertile and healthy population and the role of Sonographic biomarkers (AFC, ovarian volume) of ovarian reserve. Most of the available data is based on studies outside India. The present study evaluates the relationship of AFC in sub-fertile cases and with healthy controls. Role of ovarian volume is also evaluated and compared with AFC.

My observation indicates that the mean level of antral follicles is lower in sub-fertile patients than in fertile group. They are statistically significant. Inter-group comparison of median values of ovarian volume showed no significant difference in my study. This parameter however can be routinely measured without any added effort along with AFC. The Receiving Operating curve for AFC between sub fertile and Fertility proven women with a Area under curve =0.980, clearly indicates AFC is a very good predictor for sub fertile women. Though my data reflects that ovarian volume has no role as a bio marker of ovarian reserve, I would like to suggest routine recording and further evaluation of role of this parameter in population based data sets.

Conclusion

- The results of this study indicate that AFC is a viable 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).
- The mean AFC in South Indian women is significantly different from that noted in Western literature, mainly due to racial, geographic and socio-economic reasons.
- A cut off value of 8 may be used to prognosticate patients undergoing assessment for female factor infertility.
- On the other hand same data can be utilized for optimum patient selection for ART. This would in turn lead to a higher success rate of this technique.

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