

An Observational Clinical Study of Age on Ovarian Reserve and the Correlation of ABO Blood Grouping with Age-Specific Serum FSH Concentration

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ABSTRACT

Introduction: Childbirth is often delayed in the contemporary world in view of advancing profession and social reasons. This has led to increasing infertility. And this also has brought in many studies on age and ovarian reserves even in India. However the north-eastern part of India is demographically and geographically different from the rest of India and similar to only a small part of the world population. This study was conducted to find if the above mentioned factors have any role in the relation of age on ovarian reserve and also with the ABO blood grouping.

Material and methods: It was an observational clinical study with a duration of 3 years on patients with infertility. Descriptive and inferential statistical analysis was carried out in the present study.

Result: 80% of the study population, irrespective of the age group and blood group has basal FSH < 10mIU/ml. However correlation statistics of age with bFSH shows age (in years) of 35.02 ± 3.13 with bFSH > 10mIU/ml and have p value of 0.020. Blood group O shows FSH > 10mIU/ml and blood group A, B, AB does not manifest any relation with FSH.

Conclusion: Age has directly related with ovarian reserve represented by basal FSH, and blood group O too has direct correlation with impaired ovarian reserve.

Keywords: Basal Follicle Stimulating Hormone, Ovarian Reserve, ABO Blood Group, Infertility, Oocyte

INTRODUCTION

A woman's reproductive potential is determined by the quality and quantity of the oocytes. This is known as ovarian reserve.¹ Impaired ovarian reserve or the widely accepted diminished ovarian reserve is considered when basal follicle stimulating hormone (FSH) concentration exceeds the normal range of >10 - 12mIU/ml.^{2,3}

Basal day -3 follicle stimulating hormone, Clomiphene Citrate Challenge Test, Gonadotropin S releasing hormone agonist stimulation test (GAST), Inhibin-B, Antral Follicle Count (AFC) and Anti-mullerian Hormone (AMH) and also the sonographic imaging of the ovaries are used for testing ovarian reserves.⁴ Anti-mullerian Hormone is considered to be more sensitive than FSH in the diagnosis of Impaired Reserve. However it is generally accepted that FSH level can effectively predict the ovarian response to ovarian stimulation. FSH is also considered to be more effective than age in predicting IVF response and cycle cancellation rate, whereas age is more effective in predicting IVF pregnancy rate.⁵ The basal FSH value is defined as the serum level

during the first 2-3 days of menstrual cycle. The method for detection is simple, economical, highly reproducible and widely applied in clinical practice.⁶

El-Toukhy et al., argued that young age does not protect against the adverse effect of reduced ovarian reserve suggesting that an elevated day-3 basal FSH is associated is not only associated with a low response, but also with poor quality oocytes leading not only to reduction in pregnancy but also to a rise in miscarriage rate⁷

In the present modern days due to social and occupational reasons, childbirth is often delayed. This contributes to diminished ovarian reserves. Though there has been numerous researches on age and FSH and ovarian reserves; less has been seen and even lesser articles are found in relation to the north-eastern part of India who are demographically and geographically different than the rest of India. This study was focused once again on the relation of age to ovarian reserve and more importantly ABO blood grouping system to ovarian reserve.

MATERIAL AND METHODS

The study was conducted among patients attending the out-patient department of Obstetrics and Gynecology JNIMS Hospital, Porompat. An observational clinical study was done on random subjects with infertility. The patients were counselled and an informed and written consent was obtained before the start of the investigation. The study was conducted over a period of 3 years on 300 subjects from August 2015 till Aug 2018. Details of personal history, family history were taken and physical clinical examinations were done. Clinical investigations also include BMI (kg/m²), basal FSH, Serum estradiol, blood grouping, USG and the other routine investigations.

Inclusion criteria: married women within 25 to 40 years of age who falls under the WHO definition of infertility

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How to cite this article: Sangeeta Mayanglambam, Melody Vashum, Kanmi Ningshen. An observational clinical study of age on ovarian reserve and the correlation of ABO blood grouping with age-specific serum FSH Concentration. International Journal of Contemporary Medical Research 2018;5(12):L12-L15.

DOI: <http://dx.doi.org/10.21276/ijcmr.2018.5.12.21>

Exclusion criteria: patients who are below 25yrs of age and above 40 years of age, so that they would not interfere age-related bias into the pool of result. The exclusion criteria also include patients with polycystic ovarian syndrome, thyroid disease, adrenal disease, hyperprolactenemia and other endocrine diseases. Congenital genital tract malformation, pelvic TB, ovarian tumours, women with single ovary and those with known uterine pathology are excluded from the study.

Patients were stratified as FSH<10mIU/ml and FSH>10mIU/ml, blood grouping of A+ve, B+ve, AB+ve and O+ve.

STATISTICAL ANALYSIS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurement are presented on mean±SD and results on categorically measurements were presented in number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made. Assumption: 1- dependent variables should be normally distributed. 2- samples drawn from the population should be random, cases of the sample should not be independent.

Student T test (two tailed, independent) has been used to find the significance of the study on continuous scale between two groups (9 intergroup analysis). Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. Pearson correlation between study variables is performed to find out the degree of relationship. Suggestive significance is p value=0.05<p<0.10,

moderately significant p value=0.01<p<0.05 and strongly significant p value= <0.01.

The statistical software namely SAS9.2, SPSS 15.0 were used for the analysis of data and microsoft word and excel have been used to generate tables.

RESULT

The total no. of patients investigated was 300 with age group of 25yrs to 40 yrs having a mean± SD of 34±3.48yrs. FSH level was recorded with mean 7.90±3.34 while the S.estradiol was recorded within the range of 40 to 231 (table-1).

Patients with blood group O constitute 42% of the total study population while 28.7%, 24.3% belongs to B+ve and A+ve respectively, while AB+ve constitute a mere 5% (table-2).

Basal FSH is categorised as <10mIU/ml and >10mIU/ml. 240 of the study group i.e.80% irrespective of the age group, blood group has FSH level of <10mIU/ml (table-3).

A statistical analysis showing correlation of age, BMI and s.estradiol level according to FSH level in table 4 indicates a moderately significant association (p = 0.20) of the age group 35.02±3.13 to having diminished ovarian reserve (DOR) i.e.FSH>10mIU/ml (table-4).

A relationship between blood type O+ve and and blood group bearing A and B antigen (A+ve, B+ve, AB+ve) with FSH were observed in the above table. Statistical analysis identified a significant association of patients with FSH >10mIU/ml to blood group O+ve (p=0.047). Blood group O+ve is twice likely to show FSH>10mIU/ml than blood group B+ve although A+ve, B+ve, AB+ve could not manifest any significant relation with FSH (table-5).

DISCUSSION

Roberts et al., determined and put forward the difference between the chronological and biological age of the ovary and the premise that basal FSH measurement estimate ovarian reserve in contrast to age, which predicts oocyte quality⁸

A study on age specific serum FSH concentrations and their correlation with the outcome of ovarian stimulation by El-Shawarby SA et al., mentioned that whereas ageing has an obvious effect on oocyte quality and the subsequent ability of the embryo to implant an develop, basal FSH serves as a better indicator of the available pool of primordial follicles i.e. functional ovarian reserves.⁹ A majority of hormonal test results are subject to age-related alterations.¹⁰ Toner 2003, mentioned that distinction between the effects of age and ovarian reserve in relation to fertility is that age is better predictor of egg quality and basal FSH concentration hence is a better predictor of egg number; maintaining the close

Descriptive Statistics	Min-Max	Mean ± SD
Age in years	25.00-40.00	34.08±3.48
BMI (kg/m ²)	20.00-29.00	24.34±2.56
FSH	3.00-19.80	7.90±3.34
S.Estradiol	40.00-231.00	74.67±33.17

Table-1: Descriptive Statistics

Blood Group	No. of patients	%
A+	73	24.3
AB+	15	5.0
B+	86	28.7
O+	126	42.0
Total	300	100.0

Table-2: Blood Group

FSH	No. of patients	%
<10	240	80.0
>10	60	20.0
Total	300	100.0

Table-3: FSH levels

	FSH		Total	P value
	<10	>10		
Age in years	33.85±3.53	35.02±3.13	34.08±3.48	0.020*
BMI (kg/m ²)	24.26±2.50	24.70±2.75	24.34±2.56	0.234
S.Estradiol	62.23±11.95	124.44±43.00	74.67±33.17	<0.001**

Table-4: Correlation of age, BMI and Estradiol according to FSH levels

Blood Group	FSH		P value
	<10 (n=240)	>10 (n=60)	
A+	62(25.8%)	11(18.3%)	0.226
AB+	13(5.4%)	2(3.3%)	0.508
B+	71(29.6%)	15(25%)	0.486
O+	94(39.2%)	32(53.3%)	0.047*
A+ and AB+ (together)	75(31.3%)	13(21.7%)	0.145

Table-5: Blood Group according to FSH

association of age and ovarian reserve.¹¹

Our study also show statistically significant association ($p=0.20$) of age group 35.02 ± 3.13 to impaired ovarian reserve which is being represented by basal FSH levels. This consolidates the direct correlation of age to FSH level which is the ovarian reserve. In addition to further solidify the close association of age to ovarian reserve our study also showed that the mean age of the subjects was 34.08 ± 3.48 years and these patients had attended the clinic with complaints of infertility of which basal FSH was measured.

European Society of Human Reproductive and Embryology (ESHRE) in 2011 gave consensus on the association of age to ovarian reserve by defining "poor ovarian response" using Bologna criteria whereby it states that at least two of the following three characteristics should be present to be called poor ovarian response:

- I) advanced maternal age of >40years of age or any other risk factors for poor ovarian response
- II) previous POR
- III) an abnormal ovarian reserve test (AFC<5-7 or AMH<0.5 - 1.1ng/ml).¹²

However it is interesting to note that some investigators-Schipper et al., Perez et al., Roji et al., opined that high FSH concentration in normal ovulatory women are not related to ovarian reserve, rather a physiological cause, owing to a wide range of FSH concentrations and depending on the genotype of the FSH receptor.^{13,14,15} This concept was also agreed upon by Szafarowska M et al. Which was stated that abnormal vascularization, oxidative stress, free radical imbalance, toxic and genetic changes all contributes to the declining oocyte quality and hence ovarian reserve. But they mentioned that the above conditions are age related. Therefore age is the most well known contributing factor to diminished ovarian reserve.¹⁶

It was in 2011 when Nejat et al. presented a paper on implications of blood type for ovarian reserve where they postulated an association of ABO blood group to ovarian reserve. They found that patients with blood group O were significantly more likely to show diminished ovarian reserve than those with blood group A or AB and B.¹⁷ Differentiated expression of enzymes such as A-transferase among ABO blood group may play a role in oocyte accrual and attrition. Glycosyltransferase which is direct translation product of ABO blood group is found to maintain the terminal glycosylation of LH with galactose-4-SO₄ oligosaccharide, thereby affecting the half-life cycle of LH.¹⁸ Therefore lack of these enzymes may lead to impaired gamete formation

and hence ovarian reserve.

Genes impacting ovarian reserve have also been localized at NR5A1 gene which is in close proximity with the ABO locus and therefore more commonly inherited together. In a study conducted among women undergoing intrauterine insemination with or without ovulation; women younger than 38 years of age with blood group O was found to be associated with lower incidence of diminished ovarian reserve than women with blood group A.¹⁹ This concept is also supported by our study which showed a relationship between blood type O+ve with FSH. Statistical analysis also identified a significant association of patients with FSH >10mIU/ml to blood group O+ve ($p=0.047$). Blood group O+ve is twice likely to show impaired ovarian reserve than blood group B+ve although A+ve, B+ve, AB+ve could not manifest any significant relation with FSH. Our study also brought to the observation that patients with blood group O constitute the majority. Race and ethnicity are known to influence the frequency of different blood group. So this could suggest the possibility of ABO grouping associated with ovarian reserve.

A study on Chinese women with sub-fertility found that a higher percentage of women with diminished ovarian reserve (DOR) were blood type O, while the B antigen (blood type B or AB) is a protective factor for ovarian reserve.²⁰ The opinion and findings however are not same with everyone. Deng j et al. Conducted a meta-analysis and systemic review on ABO blood group and ovarian reserve including the studies by Nejat 2011, Timberlake 2013, Lin 2014, Sengul 2014, Mu 2016, Mouzan 2012, and Periera 2013 and concluded that the study failed to find any association between ABO blood group and ovarian reserve. They also argued that Nejat et al did not establish a set time in the menstrual cycle for obtaining samples.

CONCLUSION

This study group which was comprised of mongoloid race of the north-eastern part of India in the state of Manipur show that age has a direct correlation to ovarian reserve which is represented by basal FSH level. And that blood group O of ABO is associated with impaired ovarian reserve with an inclination towards diminished ovarian reserve. This finding is similar with studies conducted on subjects in other parts of the world but which are demographically and geographically similar, hence bringing forth its role to the relation of age and blood group O on ovarian reserve.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 14-11-2018; **Accepted:** 10-12-2018; **Published:** 22-12-2018