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To study the association of ABO blood group type with Ovarian reserve in infertile women

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Abstract
Background: ABO blood groups association with ovarian reserve had been remains controversial in previous studies. The aim of this study was to assess the association of ABO blood type with ovarian reserve in infertile women attending a tertiary care centre in North India.
Methods: This is a hospital based retrospective study of the 241 infertile women of under 40 years, who attended the infertility clinic at a tertiary care centre in North India between January 2016 and January 2018 at a tertiary care centre in North India. Patient were divided into two groups depends on the FSH levels, Group 1: FSH level <10 IU/L and Group two: FSH ≥10 IU/L. The correlation between the patients FSH level and ABO blood group were seen. Continuous variable´s presented in mean±SD while categorical variables presented in frequency (%).
Results: There was variation in age, FSH, LH, TSH and AMH levels between two groups (Group 1, FSH <10 and Group 2, FSH ≥10), which was significant (p<0.05). FSH was corelated with different ABO blood group, but it was not significant (p>0.05).
Conclusions: LH and AMH were found significantly predictors of the ovarian reserve. There was no association found between ABO blood group type with Ovarian reserve in infertile women.

Keywords: Infertility, Ovarian reserve, ABO blood group, FSH, LH, AMH

Introduction
Ovarian reserve refers to the quantity and quality of remaining oocytes, and indicative of a woman's reproductive potential [1]. Assessment of ovarian reserve, which involves testing antral follicle count and follicle stimulating hormone (FSH), anti-Mullerian hormone (AMH), and inhibin-B levels, is helpful for women who want to achieve pregnancy [2]. Recently, changes in the social environment, lifestyle and prolonged female reproductive years have led to gradual increases in female infertility [3, 4]. Many factors are related to decreased ovarian reserve (DOR) that includes age, ovarian surgery, endometriosis, chemotherapy, and abdominal radiation [5, 6]. Generally, an early follicular phase serum FSH concentration > 10 IU/L indicates an increased risk of DOR [7- 9]. The basal FSH value, defined as the serum level during the first 2-3 days of the menstrual cycle, can be used for screening, counselling and other diagnostic purposes. The method used for detection is simple, economical, highly reproducible, and widely applied in clinical practice [10].
Several biological studies have indicated that blood type and ovarian reserve may be inextricably linked. The locus for ABO gene is located on chromosome 9q34. The direct translation product of the ABO blood group gene is glycosyltransferase. FSH and luteinizing hormone (LH) receptors are heavily glycosylated proteins crucial for follicle development and maturation, and FSH receptor expression in ovarian granulosa cells functions together with activated LH receptors to promote follicular development.[11] The circulatory half-life and biologic activity of LH at the hormone receptor level are strongly affected by glycosylation.[12] Thus, it is likely that the biological activities of FSH and LH are altered by glycotransferases encoded by the O allele (those with blood type O, lack the transferase enzyme), and that DOR is a consequence of this alteration. The NR5A1 gene is located at the core of ABO gene and plays a role in transcriptional regulation in the hypothalamic-pituitary-ovary (HPO) axis. Blocking the transcription and translation of the NR5A1 gene, disturbs FSH, LH secretion and HPO axis in mice [13]. NR5A1 is expressed during almost every stage of a woman's life from fetus to adulthood. When NR5A1 expression is dysregulated, the follicles in the ovary cortex cannot mature normally and affects ovulation [14].

Recent studies have examined the relationship between blood type and ovarian reserve, but have obtained contradictory or conflicting results [16–22]. Additional studies are necessary to reconcile these conflicting findings and validating the fact. Not much studies had been done in Indian population in this regard. We therefore collected and analysed data to investigate the association between ABO blood group type and ovarian reserve.

Methods

This hospital based retrospective study was done on the women who came to infertility clinic between January 2016 and January 2018 at Department of Maternal and Reproductive Health, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India. Patient with age less than 40 years with infertility were included. Participant data was collected on proforma that includes age, body mass index (BMI), blood type, types of sub fertility, history of previous pregnancies from hospital records. Patients with incomplete data or follow up, ages were more than 40 years, history of endometriosis, ovarian surgery, chemotherapy or abdominal radiation were excluded from the study. The FSH level along with other hormones of day two of menstrual cycle were noted. Patient were divided into two groups depending on the FSH levels. Group 1 females with, FSH level <10 IU/L and Group 2, females with FSH ≥10 IU/L. Generally, an early follicular phase serum FSH concentration ≥10 IU/L indicates an increased risk of decreased ovarian reserve (DOR) [18, 19].

Statistical analysis: Normality of the continuous variables were assessed and considered normally distributed when Z score of the skewness was between ±3.29. Continuous variable´s presented in mean± standard deviation (SD) and median (Inter-quartile range" IQR") while categorical variables presented in frequency (%). Chi-square test/Fisher exact test was used to compare the proportions/test the association between two categorical variables. The predictors of the diminished ovarian reserve were evaluated using binary logistic regressions analysis. Receiver operating characteristics (ROC) curve used to calculate area under curve to identify the predicting accuracy of the independent predictors. P value <0.05 was considered as statistically significant. Data were analysed using Statistical package for social sciences, version-23 (SPSS-23, IBM, Chicago, USA).

Results

Demographic and hormonal profiles of the patients are given in table 1. Mean age (years) of the patients was 29.42±4.47 (median:29 years, range:19-40 years). Similarly mean± SD or median (inter-quartile range) of BMI, FSH, LH, Prolactin, TSH and AMH are also given. Demographic and clinical values compared between two groups (Group 1, FSH <10 and Group 2, FSH ≥10). Result showed that except body mass index and prolactin (p>0.05), for rest other variables, distribution was significantly different between two FSH groups (p<0.05) (Table 1). On study of blood group with age the most common blood group in age group 20-29 years were B+ (40.94%) followed by O+(27.77%). In age group 30-40 years the common blood group found were B+ (42.10%) followed by O+(34.21%) same as previous group [Table 2].

Association of the blood groups with Group 1, FSH <10 and Group 2, FSH ≥10) was analysed and given in Table 3. Out of total 241 patients, maximum had blood group of B+ (41.9%) followed by O+ (29.9%) and A+(17%). In 87.1% patients in Group 1, FSH was <10 (normal ovarian reserve) whereas in 12.9% in Group 2, FSH was ≥10 (decreased ovarian reserve). FSH ≥10 was present in maximum of patients with blood group B+ followed by O+. Except AB- and O-, rest for other blood groups, distribution of FSH level was significantly different (p<0.05).

Out of total (241) infertile women, 122 patients were of primary infertility. In Primary Infertility 109(89.3%) patients FSH level was <10 and 13 patients had FSH Level>10. In 119 patients had secondary infertility in whom 101 (84.8%) patient had FSH<10 and 18 patients were having FSH level > 10. There was no statistically significant difference or association between type of infertility and FSH groups (p=0.300) (Table 1). Out of the 31 patients in Group 2 with FSH ≥10, were further divided in primary (N=13) and secondary(N=18) infertility group. These two group had no statistically significant association with any blood group(p>0.05) [Table 2 and Figure 1].

In the table 4, predictor of the decrease ovarian reserve was assessed using binary logistic regression analysis. In univariate analysis, age, BMI, LH, Prolactin, TSH, AMH, blood groups and type of infertility were included. Out of this age, LH and AMH were found significant in univariate analysis. Whereas in multivariate analysis, only LH (Adjusted odds ratio=1.30, 95% CI: 1.06-1.60, p=0.011) and AMH (Adjusted odds ratio=0.56, 95% CI: 0.37-0.84, p=0.005) were found significant independent predictors for the decrease ovarian reserve (p<0.05).

As LH and AMH are significant independent predictors of the decrease ovarian reserve, resultant their DOR prediction accuracy through area under curve was observed using ROC curve. AMH [AUC=0.811, 95% CI: 0.706-0.916, p<0.001] and LH [AUC=0.661, 95% CI=0.560-0.760, p=0.004] showed that AMH was better predictor as compared to LH [0.81% vs. 0.66%, p<0.001]. For AMH value ≤1.38 [sensitivity=76.5%, specificity=79.1%] and LH value ≥5.93 [sensitivity =63.5%, specificity =52.9%] were considered as the best available cut off point to detect the decrease ovarian reserve when objective was to find out the highest sensitivity with corresponding at least >50 specificity.

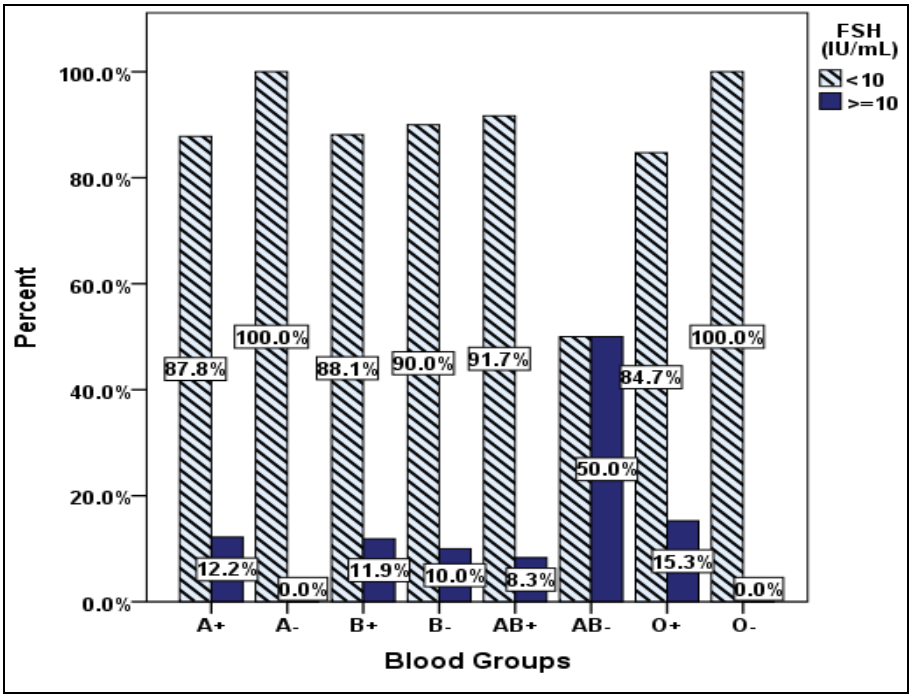

Fig 1: Distribution of FSH Levels (Group 1= FSH<10, Group 2 = FSH ≥10) in different ABO blood groups

Table 1: Baseline patients characteristics and its comparison between two study groups

Variable's	Total (n=241)	Group 1 <10 (n=210)	Group 2 ≥10 (n=31)	P value
Age (years)	29.42±4.47	28.85±4.26	33.29±3.98	<0.001
BMI	25.14±4.18	25.18±4.21	24.83±4.01	0.119
#FSH	6.66(5.30-8.0)	6.30(5.07-7.50)	12.5(11.5-16.5)	<0.001
#LH	5.92(4.22-8.25)	5.82(3.87-7.56)	7(5.39-10.6)	0.004
#Prolactin	252(140.5-410.0)	251.50(156.00-384.25)	261(32.8-358.0)	0.305
#TSH	2.64(1.85-3.60)	2.57(1.73-3.39)	3.1(2.45-4.37)	0.035
#AMH(n=89) *	2.34(1.05-6.5)	3.74(1.49-8.34)	0.84(0.29-2.08)	<0.001
Primary Infertility	122(50.6%)	109(89.3%)	13(10.6%)	0.300
Secondary Infertility	119(49,3%)	101(84.8%)	18(15.1%)	0.300

Mean±SD / #Median (Q1-Q3 "IQR") used, Unpaired t test / #Mann Whitney U test used,
in *AMH, (n≥10=17, n<10=67).
The unit of FSH(IU/L), LH(IU/L), TSH (miu/l), Prolactin (miu/l) and AMH (ng/dl) measurement are given.
p<0.05 significant

Table 2: Distribution of ABO blood groups with age

Blood Groups	Age 20-29 years (N=127)	Age 30-40 years (N=114)
A+	26(20.47%)	15(13.15%)
A-	1(0.78%)	0
B+	52(40.94%)	48(42.10%)
B-	7(5.51%)	4(3.50%)
AB+	6(4.72%)	5(4.38%)
AB-	1(0.78%)	1(0.87%)
O+	34(27.77%)	39(34.21%)
O-	0	2(1.75%)

Table 3: Distribution of the ABO blood groups in patients with FSH level and type of infertility

Blood Group		FSH levels (N=241)			Type of infertility in Group 2 FSH ≥10 (N=31)		
Type	N =241 (%)	Group 1<10 (n=210, 87.1%)	Group 2 ≥10 (n=31, 12.9%)	P Value	Primary Infertility (n=13, 41.9%)	Secondary Infertility (n=18, 58.1%)	P value
A+	41 (17)	36(17.1)	5(16.1)	<0.001	1(7.7)	4(22.2)	0.180
A-	1(0.4)	1(0.5)	0(0)	<0.001	0(0)	0(0)	--

B+	101(41.9)	89(42.4)	12(38.7)	<0.001	7(53.8)	5(27.8)	0.564
B-	10(4.1)	9(4.3)	1(3.2)	0.011	0(0)	1(5.6)	--
AB+	12(5.0)	11(5.2)	1(3.2)	0.004	0(0)	1(5.6)	--
AB-	2(0.8)	1(0.5)	1(3.2)	>0.05	1(7.7)	0(0)	--
O+	72(29.9)	61(29)	11(35.5)	<0.001	4(30.8)	7(38.9)	0.366
O-	2(0.8)	2(1)	0(0)	--	0(0)	0(0)	--
Chi-square test / Fisher exact test used, $p<0.05$ significant When frequencies were nil, corresponding significance level was not computed.							

Table 4: Binary logistic regression analysis for predictors of ovarian reserve (FSH≥10 IU/L) of patients

Binary Logistic Regression Analysis						
	Univariate Analysis			Multivariate Analysis		
Variable´s	Odds ratio	95% CI	P value	Odds ratio	95% CI	P Value
Age	1.26	1.14-1.38	<0.001	-	-	-
BMI	0.98	0.89-1.07	0.660	-	-	-
LH	1.14	1.06-1.24	0.001	1.30	1.06-1.60	0.011
Prolactin	0.99	0.99-1.00	0.197	-	-	-
TSH	1.01	0.96-1.06	0.769	-	-	-
AMH	0.57	0.38-0.87	0.009	0.56	0.37-0.84	0.005
Blood groups			0.952	-	-	-
A+	Ref.					-
B+	0.97	0.32-2.95	0.958	-	-	-
AB+	0.66	0.07-6.22	0.712	-	-	-
O+	1.30	0.42-4.04	0.652	-	-	-
#Others	1.11	0.19-6.43	0.909	-	-	-
Type of Infertility						
Primary	Ref.					
Secondary	1.49	0.70-3.21	0.302			
Only significant variables in univariate included in multivariate analysis. Outcome variable [(FSH (≥10, <10)]. #Other [A-, B-, AB-, O-] $p<0.05$ significant						

Discussion

The aim of the study was to test the association between blood group type and ovarian reserve in infertile women. One study found that women with blood type O were twice as likely to have increased baseline FSH concentrations compared to women with blood types A or AB. Additionally, in this study blood type O was associated with an increased risk of DOR, while the A antigen (blood type A or AB) was associated with a reduced risk [16]. On the contradictory another study on Chinese women found that blood type O were less likely to have DOR, while the B antigen (blood type B or AB) was a risk factor for DOR. Blood type A was not related to ovarian reserve in that study [17]. Finally, the other studies found no association between blood type and ovarian reserve. These conflicting findings may be due to racial variation between the study populations, because both blood type prevalence and ovarian reserve status differ among women of different races [21, 22].

Our study found no relationship between ABO blood type and serum FSH and AMH as a marker of ovarian reserve in patients. Furthermore, in analysis we had taken cut-off for serum FSH levels >10 m IU/ml and AMH levels < 1 ng/ml for diminished ovarian reserve. Association between ABO blood type and diminished ovarian reserve was first described by Nejat *et al.* and found that patients with blood type O had high representation of serum FSH levels >10 mIU/ml [16]. In contrast, in patients with normal ovarian reserve there was significantly higher representation of the A antigen [17]. Subsequent investigations have failed to highlight any association between blood type and serum FSH as a marker of ovarian reserve [18].

Similar to us age in relation to FSH, older age was associated with greater odds for diminished ovarian reserve [19]. AMH levels better correlate with the number of early antral follicles compared to other hormonal markers [23]. and are more specific than FSH levels at predicting oocyte yield and IVF response [24 - 26]. Our findings are consistent with the results from de Mouzon *et al.*, no relationship was found between blood groups and AMH as a marker of ovarian reserve [18, 20].

The retrospective nature of our study and the lack of analysis of potential confounders such as race, ethnicity, smoking status and prior ovarian surgery can be considered as weakness of this study. A largest study in USA stated that the highest percentages of ORh+, BRh+/ABRh+, and Rh– are present in Hispanic, Asian, and white non- Hispanic donors, respectively [27]. Besides it is seen in literature that ovarian reserve may also differ dramatically among races. The Latina and Chinese women may have lower ovarian reserve and at increased risk of early menopause in comparison to White women [28]. Women with a history of prior ovarian surgery, chemotherapy, radiatiotherapy, severe endometriosis, smoking, pelvic infection, or a strong family history of early menopause may be at an increased risk of decreased ovarian reserve [29].

However, it is encouraging to note that our results remain consistent with other studies involving multivariate analysis of potential confounders. On the basis of this study, we can postulate that the association of ABO blood type with ovarian reserve, if any, is weak at best. As this study with small number of patients, are not enough to make the finding as generalised statement that may be applicable to whole population. we suggest the bigger, high-quality, multicentric studies with large sample sizes to find more profound correlation or association of blood group with ovarian reserve.

Conclusion

The association between ABO blood groups and ovarian reserve in infertile women has been a point of controversy. The other

factors affecting ovarian function and ovarian reserve are, such as smoking, previous chemotherapy or radiotherapy, ovarian surgery, and endometriosis and they should be analysed to avoid any bias. we did not find any significant association between ovarian reserve and ABO blood group and recommend other studies with large number of patients to further strengthen the fact.

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