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The Blood Group and Ovarian Reserve Relationship

Weaam F Al Mahfooth[1*], Dhifaf H Majeed[2] and Zahra A Kareem[3]

[1]Assistant prof. department of obstetrics and gynaecology. Basrah University, college of medicine /Iraq

[2]Specialist obstetrics-gynaecology, Al Mawany teaching hospital, Iraq

[3]Specialist obstetrics-gynaecology, Basarh teaching hospital, Iraq

***Corresponding Author**

Weaam F Al Mahfooth, Assistant Professor, Department of Obstetrics and Gynaecology, Basrah University, College of Medicine, Iraq, Tel: 009647810410158; E-mail: weaamfaik@yahoo.com

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Abstract

Objective: There has been an interest in the relationship between ABO blood groups and infertility. We explored the relevance of blood type to ovarian reserve, as reflected by early follicular phase FSH levels

The design: This study was a retrospective analysis of the association between ABO blood type and ovarian reserve and included 872 women at Basra teaching for Maternity and Childhood hospital and Al mawany teaching hospital / Iraq between 2013 and 2016.

Methods: In this retrospective study, we analyzed basic characteristic and blood group data from 872 women who classified into 417 infertile women who were undergoing fertility evaluation at Basra teaching for Maternity and Childhood hospital, Basra speciality center for IVF between 2013 and 2016 fertility evaluation and 455 women who visited the labor word at Al Mawany teaching hospital between 2013 and 2016. The patients' age was procured just for those between 30 and 45 years of age. Early follicular phase serum FSH level (IU/L) was collected for infertile women then they were classified into the following two groups based on their S.FSH level:

The diminished ovarian reserve group (S.FSH≥10 IU/L) and Non- diminished ovarian reserve group (S.FSH<10 IU/L). We analyzed the distributions of basic symptoms and different blood types within these two groups to investigate the association between the blood group and ovarian reserve.

Results: among 872 women prevalence of blood groups according to the order of frequency was A (25.5%), B (28%), AB (15.9%) and O (30.6%).

There was a statistically significantly higher percentage of blood group O among those with follicle-stimulating hormone (FSH) levels ≥ 10 IU/L compared with those with FSH levels <10 IU/L. Conversely, the women with blood groups A and B had a protective effect against diminished ovarian reserve; while blood group AB had no association with ovarian reserve.

Conclusion: The O blood group appears to be associated with diminished ovarian reserve, whereas The A and B blood group appears to be protective for ovarian reserve. Further studies are needed to establish causality and identify the underlying mechanisms for the association.

Keywords: Blood Groups; Infertility; Ovarian Reserve

Introduction

Blood is an individual's complete and unchangeable identity, although almost 400 blood group antigens have been reported, the ABO and Rh have been recognized as the major clinically significant blood group antigens [1].The ABO system was the first genetic polymorphism defined in human beings, since that time the blood groups have played a prominent role in the study of human polymorphisms. Because of its easy classification into different phenotypes and different frequencies in different populations, blood groups are useful genetic markers in population studies and linkage analysis [2]. Since its introduction, the relationship to different pathologies to ABO blood groups has been of interest to researchers. Aird et al reported the relationship of blood groups to gastric cancer. Later, Solish and Gershowitz failed to find any correlation between infertility and blood groups. Recently, a predominance of blood group A was shown in patients with endometriosis [3]. Ovarian reserve, a measure that takes into account the quantity and quality of remaining oocytes, is indicative of a woman's reproductive potential [4]. Assessment of ovarian reserve, which involves testing antral follicle count (AFC) and follicle-stimulating hormone (FSH), anti-mullerian hormone (AMH), and inhibin-B levels [5], is helpful for women who want to achieve pregnancy. Generally, an early follicular phase serum FSH concentration > 10 IU/L indicates an increased risk of diminished ovarian reserve (DOR) [6]. any factors are related to DOR, including age, ovarian surgery, endometriosis, chemotherapy, and abdominal radiation [7]. In recent years, several reports have pointed to a novel association between blood group ABO and some processes related to female infertility, including diminished ovarian reserve, ovarian hyperstimulation syndrome, recurrent spontaneous abortion, and increased risk of thrombosis. It has even been hypothesized that the AB0 blood group system could be linked to ovarian reserve (OR) as reflected by early follicular phase follicle-stimulating hormone (FSH) levels [8,9]. The exact mechanism underlying the relationship between blood type and ovarian function was unclear, but haplotype variations and genetic inheritance were among the theories put forward. Unknown gene variants close to the ABO locus in chromosome 9 and associated with ovarian function may theoretically explain the correlation observed [10]. Another possible explanation was that the blood group A transferase enzyme would have a protective role for ovarian reserve by acting on the glycosylated proteins of the luteinizing hormone (LH) and FSH receptors, which play a crucial role in follicle development and maturation. Thus, the lack of this transferase enzyme (as in the case of those with blood type O) might cause a loss of such protective effect against a lower ovarian reserve [11]. Because they failed to find a link between blood group and reduced ovarian reserve, the investigators did not consider blood group to be a risk factor for diminishing ovarian reserve in clinical practice [12]. In 2014 a new study retrospectively analyzed a specific ethnic group (the Chinese population) and a larger sample of patients, the authors reported a lower incidence of diminishing ovarian reserve in women with blood group O, and a higher risk of diminishing ovarian reserve in those with the B antigen (blood group B or AB), even after performing a multivariate logistic regression analysis in which patient characteristics were taken into account. In their patient population, blood group O protected against diminishing ovarian reserve, the B antigen (blood group B or AB) was a risk factor, and blood group A was not associated [13]. On other hand, it was hypothesized that elevated risk for ovarian hyperstimulation syndrome in blood group A patients compared to women with blood group O might be due to previously observed differences in von Willebrand factor (vWf) and factor VIII concentrations.Depending on the fact of secretor genetics appears to interact with ABO genetics to influence the plasma levels of vWf, with non-secretors and non-O blood groups having the highest vWf concentrations, and the group O secretors having the lowest concentration of vWf: Ag and VIII: Ag [9,14]. We may ask whether these discrepant findings are a consequence of differences in ethnicity, sample size, study design, or ovarian reserve marker, or whether they are merely a statistical artifact [13]. Biological plausibility could help us to improve our understanding of this potential link, but no clear information about this point is given. In addition, reliable markers of ovarian reserve are lacking in the study [13], such as antimullerian hormone levels or the number of oocytes obtained in each of the blood groups studied. A prospective recording of these and other parameters that affect ovarian function, such as smoking, cause of infertility, previous chemotherapy or radiotherapy, type of ovarian surgery, the severity of ovarian diseases (endometriosis, infections), or genetic background would be of great interest, as they could be compared among the different blood groups or even excluded before comparison to determine the true association of blood group with poor ovarian function if it does indeed exist [8]. Blood type ABO may or may not be related to some aspects of female fertility. However, further studies are needed to confirm this link and to explain the underlying mechanisms. The evidence available to date is not sufficient to consider the blood group as a risk factor for DOR in clinical practice.

Material and Methods

This retrospective study was conducted on 872 women who attended the IVF center at Basrah teaching for Maternity and Childhood hospital, Al Basrah Specialty Centre for IVF and Al Mawany teaching hospital, between 2013 and 2017, after taking permission from the centers' manager. The data were collected carefully from the patients' files included name, age, parity, blood group, duration of infertility and day 2 FSH levels regarding infertile women. For this study, we only included women who were age ranges between 30 and 45 years which were obtained from the files and corrected continuously.

Women in our study were classified into two groups according to fertility state, was 455 fertile women and other groups 417 infertile women (with a history of infertility for at least two years). The infertile group is also subdivided into two groups according to ovarian reserve. Day-2 serum FSH was quantified using an auto immunoassay analyzer [Unicel Dxl 800, Beckman Coulter, USA]. The intra-assay coefficient of variation (CV) for FSH was 3.1%-4.3%, and the inter-assay CV was 4.3%-5.6%. Diminish ovarian reserve DOR was defined as a day-2 serum FSH concentration > 10IU/L by using Beckman immunoassay (Beckman Coulter). Thus the infertile women also subdivided into those with FSH level less than 10 IU/l and other with FSH level more than 10 IU/l. All infertile women were with unknown causes of infertility and had been excluded from any previous pregnancy, previous pelvic surgery, history of PCOS, irregularity of menstrual cycle and male factor for infertility.

Statistical Analysis

Data were collected onto a paper recording form from the clinic's Society for Assisted Reproductive Technology and labor word, data input worksheets, electronic medical records, and paper charts, which was subsequently entered into a secure electronic database. Statistical analyses were performed by using chi-square, p-value and SPSS version 8.1 Continuous variables are shown as mean and categorical variables are presented as counts with proportions.

Table 1: The demographic distribution of fertile and infertile women

Parameter		Fertile	Infertile
		Number [%]	Number [%]
Total number		455 [52.2]	417 [47.8]
Age(30 – 45) (Mean value)		36.04 ± 3.94	36.55 ± 3.94
Parity (Mean value)		4.6	NA
Blood group	A	131	91
	B	162	82
	AB	78	61
	O	84	183
Duration of infertility (Mean value)		NA	10.1
FSH (Mean value)		NA	8.8

NA = not applicable

Results

Informative data were available for 872 women ages 30 – 45 years (mean age 36.04 ± 3.94 regarding fertile women and 36.55 ± 3.94 regarding infertile women). The number of children for fertile women (parity) was calculated then the mean of parity was 4.6. Prevalence of blood group according to the order of frequency is presented as A, B, AB and O blood groups. Blood groups B and A were more predominant infertile women, while blood group O was less predominant infertile women. Regarding blood group AB, there was no significant difference between fertile and infertile women. The serum FSH level in mean value was 8.8 for infertile women. The duration of infertility also accounted for at least two years and the mean value was 10.1.

Table 2: Frequency distribution of blood groups in fertile and infertile women

Blood group		Group		Total	Chi	P-value
		Fertile	Infertile			
A	Count	131	91	222	5.57	0.018
	%within Bl. group	59.0%	41.0%	100.0%		
	% within Group	28.8%	21.8%	25.5%		
	% of Total	15.0%	10.4%	25.5%		
B	Count	162	82	244	27.4	0.000
	% within Bl. Group	66.4%	33.6%	100.0%		
	% within Group	35.6%	19.7%	28.0%		
	% of Total	18.6%	9.4%	28.0%		
AB	Count	78	61	139	1.03	> 0.05
	% within Bl. Group	56.1%	43.9%	100.0%		
	% within Group	17.1%	14.6%	15.9%		
	% of Total	8.9%	7.0%	15.9%		
O	Count	84	183	267	66.2	0.000
	% within Bl. Group	31.5%	68.5%	100.0%		
	% within Group	18.5%	43.9%	30.6%		
	% of Total	9.6%	21.0%	30.6%		

Pearson Chi square= 70.7; P=0.000

Blood group O has the highest overall percentage frequency (30.6%), AB blood group has the least overall percentage frequency (15.9%), While blood group A was (25.5%) and B was (28%). Representation of blood groups A, B, AB and O were comparable between the fertile and infertile women, (P-value = 0.000, chi-square = 70.7). Blood group B was more predominant among infertile women when compared with infertile women (18.6% vs. 9.4%, P = 0.000).

Regarding blood group A also was common in fertile women in comparison with infertile women (15.0% vs. 10.4% p=0.018). While blood group O was the less predominant blood group among fertile women and more predominant in infertile women (9.6% vs. 21%, P = 0.000).

Regarding blood group AB, there was no significant difference between fertile and infertile women (8.9% vs. 7%, P >0.05).

Table 3: The relationship between blood group and day 2 serum FSH level in infertile women

Blood group	FSH < 10	FSH >10	Chi Square	P value
A	63 [69.2]	28 [30.8]	12.7	0.000
B	52 [63.4]	30 [36.6]	4.66	0.031
AB	48 [75.4]	15 [24.6]	16.4	0.000
O	58 [31.7]	125 [68.3]	57.8	0.000

Chi Sq = 60.1; P=0.000

In table 3 we investigated the possible association between ovarian reserve parameters based on day 2 serum FSH level (< 10 IU/L vs > 10) for women ranging 30 – 45 years of age. We found there was a statistically significant higher percentage of blood group O among women with serum FSH level >10 IU/L as compared with those with serum FSH level < 10 IU/L. In contrast, there were statistically significantly high percentages of blood groups A and B for those with serum FSH levels < 10. However, no statistically significant difference was observed between blood group AB and ovarian reserve.

Table 4: Odd ratio after adjusting for age and study site

Blood group	Odds ratio [CI 95%]	P-value
A	1.45 [1.06- 1.97]	0.0186
B	2.26 [1.66-3.07]	<0.0001
AB	1.21 [0.84 – 1.74]	>0.05
O	0.29 [0.21-0.39]	<0.0001

This table indicated a significant positive association between infertility and the O blood group (OR 0.29 P<0.0001), There was a significant negative association between infertility and both the A blood group (OR 1.45 P=0.0186) and B blood group (OR 2.26 p <0.0001).AB blood group with non-significant association with infertility (OR 1.21 P > 0.05).

Discussion

This retrospective study has distinguished the association between blood group and ovarian reserve for many women who seeking fertility treatment. In our study, we found that the predominant blood group among 872 Iraqi women was blood group O at (30.6%), while blood group A at (25.5%), B at (28%), and AB at (15.9%). A study was done in 2014 for the frequency distribution of Iraqi people, which demonstrated that blood group O is more predominant at (49.9%), and blood group AB is less predominant at (7.6%) [16]. The predominant blood group in the united states is O at (44%) and AB at (4%) [17] While in the Chinese population the distribution of blood groups are O at 29%, A at 27%, B at 32%, and AB at 13% [18]. These changes in A, B, and O allele frequencies influence the distributions of blood groups among different populations, explain the possibility of racial and ethnic differences in blood groups and distributions account for the differences in our findings as compared with the findings of other studies. Regarding ovarian reserve, this study demonstrated that the blood group O is more predominant among infertile women (68.5 %) and there is a high likelihood of having diminished ovarian reserve (68.3 %) comparing with other blood groups. Our results were similar with Nejat et al [11], who recently reported that women with blood group O were more likely to have diminished ovarian reserve, defined by serum follicle-stimulating hormone (FSH) levels >10 mIU/ml. While these results were incompatible with Lin S et al [14] who found that blood group O was not associated with an increase in diminished ovarian reserve among Chinese women The possible explanation for this association was that, the transferases enzyme would have a protective role for ovarian reserve by acting on the glycosylated proteins of the luteinizing hormone (LH) and FSH receptors, which play a crucial role in follicle development and maturation. Thus, the lack of this transferase enzyme (as in the case of those with blood group O) might cause a loss of such protective effect against a lower ovarian reserve [19]. The results of our study regarding blood groups A and B were more predominant among fertile women in near values (55.1% and 66.39% respectively), and they at less likelihood of having diminished ovarian reserve, These results were nearly compatible with the results of Nejat et al [11] who found that blood group A provided a protective effect for ovarian reserve with same explanation of that the blood group A transferase enzyme would have a protective role for ovarian reserve [19]. The study disagreed with Lin S et al [19] who found that blood group B antigen (B and AB) was at an increased risk for diminished ovarian reserve and Blood type A was not related to ovarian reserve in that study. While in our study we found that blood group AB had no association with 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.

Our study completely had disagreed with Timberlake et

al [13] who denied any association between blood groups and ovarian reserve in 2013 in U.S. center, he studied ovarian reserve about blood group in 305 patients undergoing in vitro fertilization (IVF) and controlled for_potential confounding variables such as smoking, body mass index, endometriosis, ovarian surgery, previous pregnancy, and maternal age, resulting in neither diminish ovarian reserve (group A vs. group O), nor the number of oocytes retrieved in the IVF cycle was associated with patient blood group. There is another explanation for the observed association between blood group and ovarian reserve which include genetic inheritance. The gene products of the ABO system are glycotransferases that catalyze the transfer of carbohydrates to the H antigen, which is a precursor of the ABO blood group antigens [20,21]. The FSH and LH receptors are glycosylated proteins that are crucial for follicle development and maturation. The circulatory half-life and biological activity of LH at the hormone receptor level are strongly affected by glycosylation [22]. 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 Specific genes relevant to ovarian reserve may be linked with the ABO gene, which is located on chromosome 9 (9q34) this is a single candidate gene, NR5A1, which is in proximity to the ABO locus and recognized as relevant to ovarian reserve [23].

In conclusion, we found that blood type O was a high likelihood of having diminished ovarian reserve, while the A and B antigens were a protective factor for ovarian reserve, in Iraqi women with subfertility, suggesting that ABO blood type could be useful in evaluating ovarian reserve in clinical practice. Additional studies are needed to confirm this association and to identify the underlying mechanisms.

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