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ABO blood group impact on early follicular stimulation hormone level among subfertile women

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Abstract
The ABO blood types are correlated with several health issues, including cardiovascular ailments, immunological responses, and cancer susceptibility. Evaluation of ovarian reserve includes the antral follicle count (AFC), levels of follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin-B.
Objective: Therefore, this study aimed at determining the relationship between ABO blood group types and early follicle stimulating hormone levels among subfertile women.
Materials and Methods: The study participating a sample of 200 individuals. This cross-sectional observational research collected serum levels of early follicular stimulation hormone (FSH mIU/ml) and oestradiol (E2, pg/ml), along with demographic data regarding blood group type (A, B, AB, and O) and patient age, for female patients aged 42 years or younger (n=200) undergoing fertility evaluation at a private clinic. Serum FSH levels over 10 mIU/ml indicate decreased ovarian reserve (DOR). The data distribution for two groups of FSH levels (≤ 10 and > 10 mIU/ml) has been delineated. The analysis used IBM SPSS version 22.0. ANOVA statistical analysis comprised: Chi-square tests have been performed to compare the distribution of blood types with the worldwide population. Further attributes of the research subjects are evaluated using ANOVA. The data analysis with a significance threshold established at $p < 0.05$.
Results: The distribution of blood types, arranged by frequency, is as follows: O: 42.5%, A: 23.5%, B: 17.5%, AB: 7.5%. Modifying to the reference age group, individuals with blood type O exhibited a higher probability of FSH levels exceeding 10 mIU/mL compared to those with blood types A, B, or AB; a greater percentage of women with diminished ovarian reserve (DOR) are of blood type O, while a smaller percentage of blood types A. The A antigen (A and AB) exhibited a significant protective correlation with ovarian reserve (p = 0.000) and AB. The A blood type antigen has a significant protective correlation with ovarian reserve (P=0.000).
Conclusions: The A blood group antigen associated with defending ovarian reserve, while blood type O seems to be linked to DOR in an age-independent manner. Large sample population based longitudinal studies are warranted to confirm the cause–effect relation and the clinical significance of this association.

Keywords: Infertility, diminished ovarian reserve, blood group, FSH

Introduction
Since its discovery in the early 1900s, the ABO blood type system has been the subject of several investigations due to its correlation with cardiovascular illnesses, cancer rates, and immunological behaviors [1]. Therefore, recent research has attempted to link ABO blood type systems to reproductive health. Blood group antigens on the surface of red blood cells may effect reproductive processes via genetic or immunological pathways. Despite some claimed improvements in ovarian reserve from previous research, blood type O seems to have different amounts of reproductive hormones than blood group A [2]. This investigation might contribute to the development of the genetically based approach to reproductive health care since it showed that blood types could influence fertility [3,4]. An indication of a woman's fertility has been defined as an evaluation of the amount and quality of oocytes that are kept in her ovary [5]. It is determined that evaluating ovarian reserve by the analysis of AFC and FSH, AMH, and inhibin-B, as suggested in researches [6], is advantageous for females who may get pregnant. A heightened risk of diminished ovarian reserve (DOR) has been associated with an FSH level over 10 IU/L during the early follicular phase [7,8]. DOR is associated with many factors: The patient's age, endometriosis, prior ovarian surgery,

chemotherapy, and abdominal radiation constitute the medical risk factors [9,10]. Recent investigations investigating the correlation between blood type and ovarian reserve yielded unreliable findings [11, 12]. Two of these studies suggested a potential relationship between blood type and ovarian reserve, however the nature of this relationship remains unclear [11,13]. None of the remaining trials identified any effect on ovarian reserve or blood type [12,14]. Further study is necessary to reconcile these conflicting findings. To ascertain the correlation between blood type and ovarian reserve, we obtained data from our facility.

Materials and Methods

Participants in this research were those who, between February 2021 and October 2023, visited the private clinic in Wasit, Al-Kut in Iraq for assessment and treatment related to infertility. Women more than 45 years old, male factor infertility and infertility caused by tubal factors were not included. Included cases were women under 45 years old with ovarian, endometrial, and uterine factors contributing to infertility. Oestradiol (E2, pg/ml) and baseline serum FSH (mIU/ml) levels were measured, along with blood types A, B, AB, and O. As a preclinical practice guideline, ovarian reserve was expressed as early follicular FSH level 10 mIU/ml as acutoff value for each individual. In accordance with the FSH level, we separated the patients into two groups: Group I (FSH ≤ 10 mIU/ml) and Group II (FSH>10 mIU/ml). Between groups I and II, all of the research participants' traits and blood group types were compared. The statistical software SPSS version 22.0 was used to analyse the data. ANOVA statistical analysis included Chi-square tests to evaluate blood group distribution. To compare additional research participant characteristics between groups, use ANOVA testing. At $P < 0.05$, statistical significance was established.

Results

Demographic Data of the Study Participants

The mean age of the study participant was (30.92± 5.88) years, the mean BMI participant was (26.30±2.63), and the mean FSH level was (7.30 ± 3.84 mIU/L). The mean E2 level was (40.76 ± 10.83(pg/ ml)). The mean duration of infertility (years) was(6.3±3.63), the type of infertility; (110(55%) was primary while secondary infertility was (90(45%)).Regarding the female causes of infertility; ovarian factors constitute about (176(88%)) while endometrial factors constitute about (24(12%)) as shown in (Table 1). When we test FSH levels in term of above or below 10 mIU/L about (n=132 participants had FSH level ≤ 10 mIU/L which constitute about (66%) while (n= 68 participants had FSH level > 10 mIU/L which constitute about (34 7.30 ± 3.84%) as shown (in Figure 1).

Table 1: Demographic Data of the Study Participants

Variables		N= (200)
Age (Years)	(Mean ± Standard Deviation)	30.92± 5.88
BMI (kg/m^2)	(Mean ± Standard Deviation)	26.30±2.63
FSH (mIU/ml)	(Mean ± Standard Deviation)	7.30 ± 3.84
E2 (pg/ ml)	(Mean ± Standard Deviation)	40.76 ± 10.83
Duration of infertility(years)	(Mean ± Standard Deviation)	6.3±3.63
Type of infertility		
Primary	Number /Percentage	110(55%)
Secondary	Number/Percentage	90(45%)
Causes of Female factors infertility		
Ovarian Factors	Number/Percentage	176(88%)
Endometrial and Uterine Factors	Number/Percentage	24(12%)

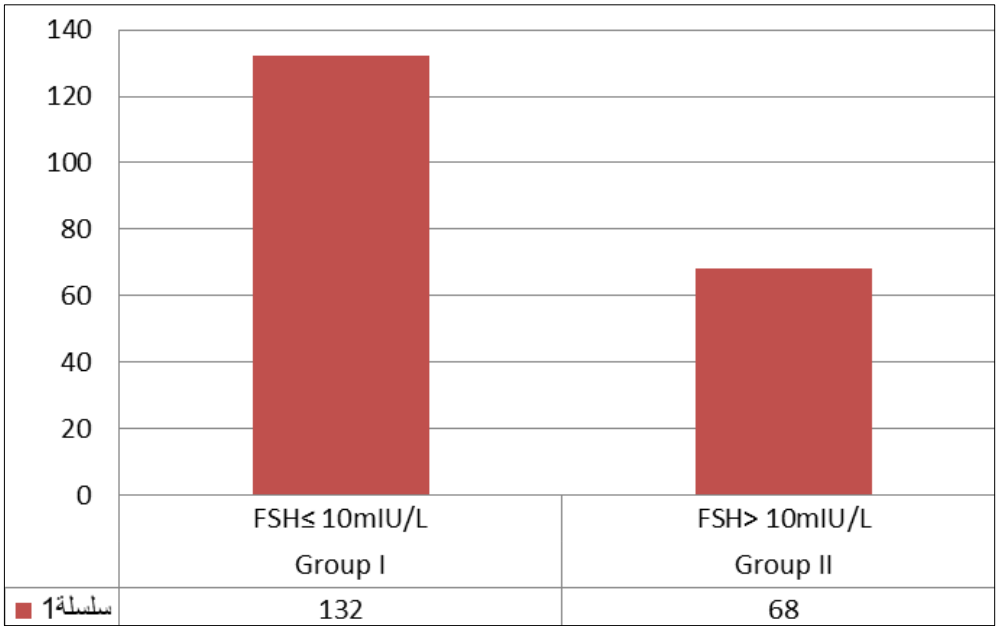

Figure 1: The Distribution of the Study Participants According to FSH Levels.

Blood Group Distribution

Table 2 and Figure 2: Summarizes the distribution of blood groups, showing that blood group O was the most prevalent (85 individuals 42.5%), followed by blood groups A (65 (23.5%)), B (35(17.5%)), and AB (15 (7.5%)). P value show significant differences between the groups (*P*=0.000).

Table 2: The distribution of blood groups

Blood Group	Frequency	Percentage	P value
A	65	23.5%	0.000*
B	35	17.5%	
AB	15	7.5%	
O	85	42.5%	
*: significance $P < 0.05$			

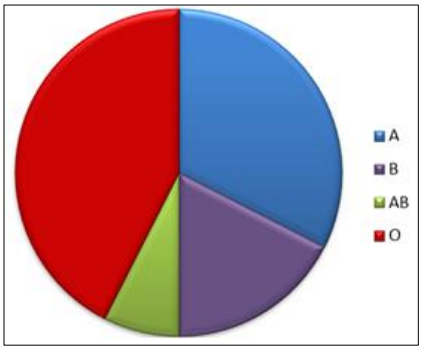

Figure 2: Distribution of Blood Groups Among the Study Participants

Characteristics of study participants according to the level of FSH

In comparison of characteristics of study participants according to the level of FSH between group I (FSH≤ 10 mIU/L) and group II(FSH > 10 mIU/L); The mean age of the study participant was (30.8±5.39 and 30.4±5.20) years respectively with no significant difference (*P*= 0.244), The mean BMI participant was (26.20±2.83 and 26.50±2.72 kg/m^2) respectively also with no significant difference (*P*= 0.239). The mean E2 level was 40.78 ± 10.38 and 40.63 ± 10.32 (pg/ ml)) respectively with no significant difference (*P*= 0.544).The mean duration of infertility (years) was(6.1±3.61 and 6.2±3.58) respectively also with no significant difference (*P* = 0.502), There were no significant differences in the types of infertility(*P*=0.067),also there were no significant differences in the causes of infertility (*P*=0.538) between the groups. Regarding the blood groups distribution between group I and II There were highly significant differences between the groups (*P*= 0.000) with the highest frequency of blood group O on group II (30 (44.11%) followed by blood group B (15(22.05%)); AB (12(17.64%)) while the lowest frequency was in blood group A (11(16.17%)). A antigen vary significantly between the 2 groups with the highest number in group I (57(43.18%))and *P* =0.000) While there was no significance differences in B antigen between the two groups with the highest number in group II (27(39.7%)) and (*P* =0.224) as shown in (Table 3).

Table 3: Characteristics of Study Participants According to the Level of FSH

Variable		Group I FSH≤ 10	Group II FSH>10	P value
Age (Years)	(Mean ± Standard Deviation)	30.8±5.39	30.4±5.20	0.244
BMI (kg/m^2)	(Mean ± Standard Deviation)	26.20±2.83	26.50±2.72	0.239
E2 (pg/ ml)	(Mean ± Standard Deviation)	40.78 ± 10.38	40.63 ± 10.32	0.544
Duration of infertility(years)	(Mean ± Standard Deviation)	6.1±3.61	6.2±3.58	0.502
Type of infertility				
Primary	Number /Percentage	60(45.5%)	50(73.5%)	0.067
Secondary	Number/Percentage	72 (54.5%)	18(26.5%)	
Causes of Female factors infertility				
Ovarian Factors	Number/Percentage	118 (89.4 %)	58 (85.3%)	0.538
Endometrial and Uterine Factors	Number/Percentage	14(10.6 %)	10 (14.7%)	
Blood group A	Number/Percentage	54(40.9%)	11(16.17%)	0.000*
Blood group B	Number/Percentage	20(15.15%)	15(22.05%)	
Blood group AB	Number/Percentage	3(2.27%)	12(17.64%)	
Blood group O	Number/Percentage	55(41.66%)	30 (44.11%)	
A antigen (A and AB)	Number/Percentage	57(43.18%)	23(33.82%)	0.000*
B antigen (B and AB)	Number/Percentage	23(17.42%)	27(39.7%)	0.224
*: significance $P < 0.05$				

Discussion

The impact of blood group selection is caused by factors such as the population groups, migration frequency and ambient geographical variables. When it comes to blood type sensitivity. Awareness is helpful in storing early knowledge about the illnesses associated with blood groups, particularly the disorders that link blood groups to ovarian reserve and subfertility. A test called ovarian reserve indicates the amount and quality of eggs a woman has available for conception as well as the several known and unknown variables that affect it. Ovarian reserve may or may not be impacted by the association between ABO blood type and other infertility mechanisms. The population distribution from figures 2, and table 2 reveals that the blood group distribution among research participants was extremely significant, with the allelic frequency of blood group of being higher than other blood types. Thus, the simulated data's universality based on population data (15,16). Although we discovered that ABO blood type is linked to a number of infertility processes, there is currently a dearth of information in the literature about the relationship, or lack of relation between ABO blood type and ovarian reserve.

The patients in our research had a significantly distinct blood group distribution, with blood group O having a higher allelic frequency than the other blood types. It was discovered that the current study's simulated data distribution matched the distribution of certain blood types in the general population. Additionally, a single locus across the ninth long arm of chromosome 9 has numerous alleles of ABO blood types, which are genetically transmitted as Mendelian traits pattern (17). There are primarily three

kinds of alleles in the ABO gene: Since it lacks an antigen, it is classified as belonging to group O. I^A carries a type A antigen, while I^B expresses a type B antigen, with I standing for iso-agglutinogen. Only ii persons have the O blood type, and I^A and I^B are both dominant over I. Due to co-dominance, an I^A I^B person possesses both phenotypes and is classified as having blood group AB (15,16).

The demographic parameters of the FSH ≤10 mIU/Ml, and FSH >10 mIU/mL groups did not vary statistically significantly in terms of mean age, BMI, duration of subfertility, type, and causes of subfertility, which were in similarity to Hazarika S *et al*., (18). There is an age-independent association between blood type O and biochemical DOR, according to our analysis of the differences between the FSH ≤10 mIU/mL and FSH >10 mIU/mL groups on blood type subgroups and A antigen (A and AB) using the Chi-square test. Furthermore, we verified that women with blood types A or AB were less likely than those with blood types O to have DOR. Therefore, we found that peripheral FSH levels were considerably greater among women with O blood type at baseline. In line with Binder *et al*.,'s findings that OHSS is more likely to be seen after ovarian stimulation in infertile women with blood type A, we have recently discovered that ovarian reserve in infertile women is related to blood type. It is not surprising that we found that the A antigen lowers the risk of DOR based on the results of this study, which are consistent with Nejat *et al*., (21). This is similar to Binder *et al*., (19,20) who described blood type A as being relatively associated with elevated ovarian response, a characteristic thought to be in direct contradiction with DOR.

Since the mechanism explaining the impact of ABO system on DOR is not well understood, there are many probable ideas. The location of the ABO gene on chromosome 9 which has 3 alleles; A, B, and O. The ABO system produces glycotransferases who is responsible for carbohydrates transmission to the antigen H, who is the ABO blood types antigens originator (22, 23), making the A and B antigens, individually (24, 25). A glycosyltransferase (A transferase) codes the A allele that is responsible for the allocation of N-acetylgalactosamine to the antigen H, creating the antigen A. Also, in the same manner, a glycosyltransferase (B transferase) codes the B allele that is responsible for the transmission of galactose into the antigen H, making the antigen B. A 258-guanine is a unique O allele base deletion, in the coding area nearby to the protein N terminus. The creation of an enzymatically lazy protein by O allele departure the antigen H unaffected on the O type RBCs (24). The antigens A and B could be present on the cell membranes of a different of cells, like epithelial cells. It is indefinite if the antigen H antigen is found in ovarian cells (26).

Considering that blood type A transferase seems to provide protection against DOR, it is plausible to assume that the enzyme may influence gamete accumulation and/or depletion. Moreover, the absence of A transferase activity, seen in individuals with blood type O, may adversely affect these processes. The follicle stimulating hormone receptor (FSH-R) and the luteinizing hormone receptor (LH-R) are extensively glycosylated proteins that are crucial for follicular development and maturation. This situation is significant as it demonstrates the reduced ovulation frequency in mice lacking the glycosyltransferase N-acetylglucosaminyltransferase specifically in the oocytes (27).

The FSH and LH receptors, unique glycoproteins located on the surface of granulosa cells, are crucial for follicular growth. Glycosylation significantly affects the biological activity of hormone receptors for LH and the hormone's half-life in the circulatory system (28). It has been posited that glycotransferases linked to the O allele influence the physiological functions of both FSH and LH concurrently. This occurs when people with blood type O lack the transferase gene, leading to a diminished ovarian reserve. Considering the genetic component, the relationship among ovarian reserve, blood type, and heredity may be elucidated more effectively. Two genes implicated in ovarian function include NR5A1 and TGFBR1. Both genes are situated on chromosome 9q34, in close proximity to the ABO locus. The likelihood of co-inheritance with ABO is increased since recombination often occurs between these genes and the ABO type genes (29,30). Due to the capacity of genes reduced to phased haplotypes to affect the structure and amounts of other proteins (31,32), the probability of co-inheriting certain allele combinations may increase. Furthermore, other associates identified that certain genetic changes, including modifications to the FMR1 gene and polymorphisms in the FSH receptor, are associated with elevated levels of FSH as reported by the researchers (33,34). Further research is necessary to ascertain the impact of these pathways on the relationship between ovarian reserve and blood type.

The research lacked sufficient power and size of sample, preventing to examine precisely the relationship between ABO blood type and ovarian reserve, while considering other significant factors such as age, AFC, BMI, and subfertility classification. I am exhibiting kindness and generosity. However, other substantial constraints need resolution. Initially, first the diagnosis of DOR was only based on FSH levels; however, to ensure that hormone levels in individuals during the early follicular phase were within the normal range, E2 was concurrently assessed to confirm their alignment with the typical range for early follicular phase hormones. This was executed to guarantee that the levels were adequately managed. Secondly, given the research only included women seeking treatment for subfertility, the results may not be applicable to the broader community. The third problem of the research is its failure to investigate the smoking habits of the patients, even though smoking is not prevalent among Iraqi women. The levels of AMH were not assessed in this study; thus, the relationship between blood type and AMH levels should be clarified in future prospective research. Blood type O is correlated with a heightened risk of decreased ovarian reserve (DOR), while the A antigen is connected with the preservation of ovarian reserve in subfertile Iraqi women. This evidence suggests that ABO blood type may be relevant in clinical assessments of ovarian reserve. Further study is essential to validate this conclusion and clarify the underlying operational processes.

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