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Preconception Immunoglobulins and Complements as Potential Biomarkers in Unexplained Female Infertility in Saudi Arabia

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Abstract

Background: Immunological abnormalities are currently under scrutiny to potentially unravel the etiology of frustrating cases of unexplained female infertility (UFI).

Objectives: To explore the prevalence of immunological abnormalities in the levels of total immunoglobulins and complements in the cases of UFI.

Methods: Females with a history of UFI were included in this cross sectional study. They were consulted at the clinical immunology clinic at the King Abdulaziz University Hospital (KAUH). Their demographics, clinical features, total immunoglobulins and complements tests results were collected and analyzed for any relationship.

Results: One hundred and twenty-one cases of UFI with an average age of 34 ± 5.6 (range from 23 to 49 years old) were studied. Secondary infertility was predominant in 99 cases (81.8%). An overall prevalence of at least one abnormal level of total immunoglobulins or complements was found in 65 cases (55.1%). The predominant immunological abnormalities were elevated levels of immunoglobulins (hypergammaglobulinemia) in 51 cases (43.2%), high IgG in 26 cases (22%), high IgA in 14 cases (11.9%), and high IgM in 11 cases (9.3%). This was followed by elevated levels of complements (hypercomplementemia) in C4 in nine cases (8.5%). *A significant association was found between high C4 group and some parameters of infertility, including primary infertility ($p = 0.005$), no pregnancy ($p = 0.001$), no abortion ($p = 0.047$), in comparison to normal C4 group.*

Moreover, a statistically significant association was found between high IgA group and abortion in comparison to normal IgA group (p = 0.054).

Conclusion: At least one abnormal level of total immunoglobulins or complements was detected in more than half of the UFI cases. The commonest abnormalities were hypergammaglobulinemia (IgG, IgM, IgA) and hypercomplementenemia (C4), which showed a potential association with some infertility parameters. These findings may encourage the screening of general immunological tests to explore promising new immunopathology in UFI.

Introduction

Unexplained female infertility (UFI) is a devastating obstetrical condition that affects females who are unable to conceive, without any definitive causes found despite extensive investigations and interventions [1, 2]. The approach to UFI is continuously being updated, as the latest evidence describes different potential etiologies with clinical links, including immunological factors [2].

Immunological responses of the uterine mucosa to developing embryos are well regulated, and a successful pregnancy requires proper immune system adaptation for the fetus and placenta [3, 2]. Approximately 20% of couples of reproductive age are affected by immune infertility, making it a significant health concern [3].

Immunoglobulins are vital for any immunologic evaluation to reflect the function of humoral immunity [4].A few studies have shown that a successful pregnancy is associated with increased total IgG production in the first trimester, followed by decreased total immunoglobulin concentrations in the second and third trimesters, which results from the immunomodulation of a healthy pregnancy [5,6].

The complement system consists of a series of proteolytic enzymes and regulatory proteins that play a positive role in various pregnancy stages, such as implantation, fetal development, and labor [7]. However, an imbalance in the complement system has been detected in pregnancy complications, and this can induce unfavorable effects on both the pregnant mother and her fetus [8,7].

Although most international reproductive and obstetric societies agree that successful conception is influenced by a healthy immune system, routine immunological investigations to explore female infertility is not recommended [9].Nevertheless, several societies recommend some immunological testing (mainly autoantibodies) for patients with recurrent pregnancy loss [10]. Recently, some societies have suggested some immunological testing for recurrent implantation failure, but with limited evidence or for clinical research purposes [11,12]. To date, there are no recommendations about testing for total immunoglobulins and complements in most reproductive societies in UFI.

However, in the face of underestimated abnormalities, general immunological laboratory investigations are seldom conducted in infertility centers in the increasing number of cases with UFI. Therefore, this research was conducted to search the prevalence of any possible abnormalities in the levels of total immunoglobulins and complements as biomarkers in patients with UFI in the Kingdom of Saudi Arabia.

Methods

This project was a retreospective cross-sectional clinical study. It was carried out on patients with UFI who attended the clinical immunology clinic at the King Abdulaziz University Hospital (KAUH) over a period of four months, from May to August 2022. The KAUH is a tertiary referral center and a large teaching center with 800 beds, located in Jeddah city in the Western zone of the Kingdom of Saudi

Arabia.

This study was authorized by the Unit of the Biomedical Ethics Research Committee at KAUH, with a reference number of 331-22. Participants were enlightened about the purposes and procedures of the study, and participation was voluntary and without any offered incentives. A verbal consent was acquired from all participants before any collection of research data.

The inclusion criteria was specified for all participating females with unexplained infertility aged 18 to 50 years old who were consulted by different infertility specialists to identify any potential immunological etiologies. Other possible common causes of infertility (anatomical, genetic, and male partner factors) were excluded. Based on the World Health Organization (WHO), primary infertility occurs when a woman has never achieved a pregnancy, and secondary infertility is when at least one prior pregnancy has been achieved [13].

The criteria for exclusion were any females complainig of infertility with known common etiologies other than disturbed immunological tests, those with deficient immunoglobulins or complements laboratory results, and those who missed follow-ups.

The patients' demographic, clinical, and laboratory information were recorded from the electronic files of medical records. Data recording was performed with Google spreadsheets for documenting the patients' demographic data and clinical details, which included type of infertility, pregnancies number, living children, preterm labors, abortions, stillbirths, and assisted reproductive techniques, including in-vitro fertilizations.

Thereafter, the laboratory results of five basic immunological tests on the serum of the included patients that was taken before attempting pregnancy were collected. These were total immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin E (IgE), complement 3 (C3), and complement 4 (C4). The results of the immunological tests were obtained from the immunology laboratory at the laboratories of KAUH.

A descriptive statistical analysis was performed for the included cases. Frequency number and percentage were extrapolated for categorical factors. The means with standard deviation were computed for the continuous variables. Then, the associations between the different collected variables were measured by the chi-square test. All p-values of < 0.05 were accounted as statistically significant. The software of Statistical Package for Social Sciences (SPSS) version 23 (Armonk, NY: IBM Corporation, USA) was utilized for all data evaluations

This trial was approved by the Research Committee of the Unit of Biomedical Ethics at KAUH with a reference number of 331-22. All participants were educated about the aims and methods of the project. Participation process was voluntary andwithout any offered incentives. From each participant a verbal consent was obtained before any data collection.

Results

A total of 136 cases with UFI, referred from different specialists in infertility across Saudi Arabia, were enrolled from the clinical immunology clinic at KAUH. Of these, 15 cases were excluded, nine because of a loss of revisit, and 6 cases for incomplete laboratory data results. In total, 121 female cases fulfilled the inclusion criteria and provided consent for this study. The ages of participants ranged from 18 to 49 (mean age of 33.9 ± SD 5.6) years old.

The nationalities data of the studied patients were; 103 cases (85.1%) Saudi citizens, and 18 cases

(14.9%) non-Saudi residents. Regarding the city of cases's residence, 70 (57.9%) from Jeddah, 10 (8.2%) from Makkah, 10 (8.2%) from Taif, and 31 (25.6%) from other cities of Saudi Arabia (Table 1).

The background data of infertility showed that secondary infertility was predominant and had been diagnosed in 99 cases (81.8%). There were 74 cases (61.2%) who had no living children, and 47 (38.8%) who had at least one living child. At least one abortion was a prominent feature in 87 cases (71.9%), while 34 cases (28.1%) had no abortions. Regarding IVF procedures, 67 cases (55.4%) had received at least one intracytoplasmic semen injection (ICSI), and 23 cases (19%) had received at least one intrauterine insemination (IUI) (Table 1).

At least one abnormal level of any of the five biomarkers of total immunoglobulins or complements was found in 65 cases, equivalent to 55.1% of the study group. High immunoglobulin levels (hypergammaglobulinemia) were the commonest abnormal immunological marker, including high IgG in 26 patients (22%), followed by high IgA in 14 patients (11.9%), and high IgM in 11 patients (9.3%) (Table 2). The next most common immunological abnormality marker was elevated levels of complements (hypercomplementemia) in 10 cases (9.4%), mainly high C4 in nine of these 10 cases (8.5%) (Table 2). However, abnormally low levels of immunological markers were rare in the studied group, including low C4 in two cases (1.7%), low IgG in one case (0.8%) and low IgM in one case (0.8%).

A statistically significant association was detected between the high C4 group and some parameters of infertility, including primary infertility ($p = 0.005$), no pregnancy ($p = 0.001$) and no abortion ($p = 0.047$), more so than in the normal group (Tables 3 and 4). Moreover, the high IgA group was nearly significantly more associated with a history of at least one abortion than the normal group ($p = 0.054$) (Table 4).

In a subgroup analysis based on the age of the patients (if less than or equal to 35 years old versus older than 35 years old), there were some statistically significant associations. The high IgG group was significantly more associated with a history of no abortion than the normal group ($p = 0.026$). Moreover, the high C4 group was significantly associated with primary infertility ($p = 0.006$), no pregnancy ($p = 0.006$), and no abortion ($p = 0.031$) more than the normal group. In addition, the high IgG group was nearly significantly associated with primary infertility ($p = 0.054$) and no pregnancy ($p = 0.056$), more so than the normal group.

Discussion

UFI, which is mainly associated with repeated abortions or implantation failures, represents an extremely challenging and distressing topic in the field of reproductive medicine. Moreover it places a significant financial and psychological burden on the involoved couples. Recent publications have advocated that an overactive immune system, such as an autoimmune disorder in some women, may expand the struggling of falling pregnant or recurrent abortions risk [14]. This advocates a potential greater chance of success through the evaluation of the immune system and applying individualized immune based treatments.

In this study, five different basic immunological laboratory biomarkers were explored in females with UFI. Interestingly, over half of the studied group had at least one abnormal test result for any of the five biomarkers of immunoglobulins or complements. A recent study measured the same five biomarkers, but during the first trimester [15].Up to our knowledge, this study is the first published research that evaluated these five biomarkers of immunoglobulin and complements together before pregnancy.

Table 1. Sociodemographic characteristics and infertility background.ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination.

Parameter	Mean	SD	Minimum	Maximum	Subgroups	n	%
Age	33.95	5.57	23.00	49.00	<35 >35	68 53	56.2 43.8
Marital Status Duration					≤10 years > 10 years	71 50	58.7 41.3
Nationality					Saudi Non Saudi	103 18	85.1 14.9
City					Jeddah Other City	70 51	57.9 42.1
Infertility type					Primary infertility Secondary infertility	22 99	18.2 81.8
No. of Living children	0.79	1.20	0.00	5.00	no child At least one living children	74 47	61.2 38.8
No. of Preterm labors	0.09	0.39	0.00	3.00	no preterm labor at least one preterm	113 8	93.4 6.6
No. of Pregnancies	3.40	3.25	0.00	14.00	no pregnancy at least one pregnancy	23 98	19.0 81.0
No. of Abortions	2.44	2.75	0.00	14.00	no abortion at least one abortion	34 87	28.1 71.9

No. of Stillbirth	0.11	0.40	0.00	3.00	No stillbirth At least one stillbirth	111 10	91.7 8.3
Intracytoplasmicsperm injection (ICSI)	1.51	1.87	0.00	10.00	No ICSI did one icsi or more	54 67	44.6 55.4
Intrauterine insemination (IUI)	0.37	0.90	0.00	4.00	No IUI Did one IUI or more	98 23	81.0 19.0

Table 2. Auto-Immunological antibodies laboratory tests according to the prevalence

	Normal		High
	N	%	N
Total IgA	104	88.1%	14
Total IgG	92	78.0%	26
Total IgM	107	90.7%	11
Hypergammaglobulinemia	84	69.4%	37
Complement C3	105	99.1%	1

In this study, the most predominant immunological abnormality was the increased levels of immunoglo bulins (hypergammaglobulinemia), mainly IgG, followed by IgA and IgM, in nearly half of the studied group. Hypergammaglobulinemia is seen in some infections, inflammatory diseases, autoimmune conditions, and plasma cell disorders [4,16]. The impacts of hypergammaglobulinemia on infertility, IVF success, and pregnancy are not yet clearly defined, but if these immunoglobulins coexist with autoantibodies, they may impair fertility [14,17].

This study revealed a potential association between high IgG and a history of (primary infertility, no pregnancy and no abortion in younger age groups) and a near association between high IgA and a history of abortion. Preconception hypergammaglobulinemia was suggested as a risk factor for low pregnancy rates with IVF [18]. Contrary to another study, there was no relationship found between preconception immunoglobulins and recurrent abortions [19].

As expected, in this study, low levels of immunoglobulins (hypogammaglobulinemia) were found to be rare, with only one case of low IgG and one case of low IgM. Hypogammaglobulinemia is an uncommon clinical finding associated with some rare immunodeficiency disorders [4,16]. Reduced levels of IgG in the first trimester have been linked to recurrent abortions [20].

The second most predominant immunological abnormality found was high levels of complements, mainly high C4, in 9.4% of the studied group. Hypercomplementemia is seen in many inflammatory

Table 3. Immunoglobulins and complements correlation with sociodemographic characteristics and infertility typeIgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M.

		Age			Maritual Status Duration			Infertility type		
		<=35	>-35	p-value	<-10 years	>10 years	p-value	primary infertility	Second-ary in-fertility	p-value
Total IGA	Normal	62 59.60%	45 40.4%	0.234	64 61.5%	40 38.5%	0.182	20 19.2%	84 80.8%	0.241
	High	6 42.9%	8 57.1%		6 61.5%	8 3 8.5%		1 7.1%	13 92.9%	
Total IGG	Normal	54 58.7%	38 41.3%	0.659	56 60.9%	36 39.1%	0.52	14 15.2%	78 84.8%	0.139
	High	14 53.8%	12 46.2%		14 53.8%	12 46.2%		7 26.9%	19 73.1%	
Total IGM	Normal	61 57.0%	46 43.0%	0.758	64 59.8%	43 40.2%	0.756	18 16.8%	89 83.2%	0.306
	High	7 63.60%	4 36.4%		6 54.5%	5 45.5%		3 27.3%	8 72.7%	
Complement c3	Normal	60 57.1%	45 42.9%	-	61 58.1%	44 41.9%	-	17 16.2%	88 83.8%	-
	High	0 0.0%	1 100.0%		0 0.0%	1 100.0%		0 0.0%	1 100.0%	
Complement C4	Normal	55 56.7%	42 43.3%	0.999	55 56.7%	42 43.3%	0.73	12 12.4%	85 87.6%	0.005
	High	5 55.6%	4 44.4%		6 66.7%	3 33.3%		5 55.6%	4 44.4%	

Table 4. Immunoglobulins and complements correlation with sociodemographic characteristics and infertility background. IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; IUI: intrauterine insemination; ICSI: intracytoplasmic sperm injection.

		No. of Pregnancies			No. of Abortions			No. of Stillbirth			ICSI			IUI		
		no pregnancy	east one pregna	p-value	no abortion	least one abortio	p-value	no stillbirth	least one stillbirt	p-value	no ICSI	did one ICSI or more	p-value	no IUI	did one IUI or more	p-value
IGA	Normal	21 20.2%	83 79.8%	0.239	32 30.8%	72 69.2%	0.054	96 92.3%	8 7.7%	0.942	48 46.2%	56 53.8%	0.213	82 78.8%	22 21.2%	0.214
	High	1 7.1%	13 92.9%		1 7.1%	13 92.9%		13 92.9%	1 7.1%		4 28.6%	10 71.4%		13 92.9%	1 7.1%	
IGG	Normal	15 16.3%	77 83.7%	0.220	24 26.1%	68 73.9%	0.392	85 92.4%	7 7.6%	0.989	42 45.7%	50 54.3%	0.514	73 79.3%	19 20.7%	0.549
	High	7 26.9%	19 73.1%		9 34.6%	17 65.4%		24 92.3%	2 7.7%		10 38.5%	16 61.5%		22 84.6%	4 15.4%	
IGM	Normal	19 17.8%	88 82.2%	0.440	29 27.1%	78 72.9%	0.515	99 92.5%	8 7.5%	0.848	47 43.9%	60 56.1%	0.922	85 79.4%	22 20.6%	0.360
	High	3 27.3%	8 72.7%		4 36.4%	7 63.6%		10 90.9%	1 9.1%		5 45.5%	6 54.5%		10 90.9%	1 9.1%	
C3	Normal	18 17.1%	87 82.9%	0.650	29 27.6%	76 72.4%	0.999	98 93.3%	7 6.7%	0.075	48 45.7%	57 54.3%	0.999	84 80.0%	21 20.0%	0.999
	High	0 0.0%	1 100.0%		0 0.0%	1 100.0%		0 0.0%	1 100.0%		0 0.0%	1 100.0%		1 100.0%	0 0.0%	
C4	Normal	13 13.4%	84 86.6%	0.001	24 24.7%	73 75.3%	0.047	90 92.8%	7 7.2%	0.672	46 47.4%	51 52.6%	0.146	78 80.4%	19 19.6%	0.850
	High	5 55.60%	4 44.40%		5 55.6%	4 44.4%		8 88.9%	1 11.1%		2 22.2%	77.8%		7 77.8%	2 22.2%	

disorders as acute phase reactants [4,16]. Interestingly, the group studied in this investigation showed a relationship between preconception high C4 and a history of primary infertility, no pregnancy, and no abortion. There are few studies that have linked preconception hypercomplementemia and recurrent abortions and suggest that it may predict subsequent abortion [19,21].

In this studied group, hypocomplementemia was rare; low C4 was only detected in two cases (1.7%), while no participant had low C3, which is less than what has been reported in the literature. There are many studies that document preconception hypocomplementemia, more with C4 than C3, with recurrent abortions at somewhat higher rates (6–10%) and more if there are associated autoantibodies [22,23,24,25]. Hypocomplementemia is seen in immune complex diseases, which indicate consumption and disease activity or, rarely, a genetic deficiency[4,16].

This research project had a few limitations, such as the use of convenient sampling from a specific clinical immunology clinic, a few deficient patient data points, and a small sample size of cases. Hence, interpreting these immunological investigations in cases with UFI requires further large-scale, highly standard-controlled research projects in the future.

The detection of an abnormality in any of the general immunological investigations may help in the establishment of a guideline as to when and in which backgrounds of infertility to order and consider these immunological biomarkers. This might shift the perspective of experts in the field of infertility to establishing a proper clinical link between the immune system and the potential causes of UFI.

In conclusion, this study focused on the prevalence of five general immune biomarkers in a convenient sample of patients with UFI. Abnormal levels of at least one immunoglobulin or complement were a common finding in more than half of these patients. Among these, high immunoglobulins (IgG, IgA, IgM) and high C4 were the predominant immunological abnormalities. A potential relationship between high IgG, IgA, and C4 and lower pregnancy rates was noted. Identifying abnormal general immune responses of the mother to her fetus may advance the clinical investigational approach of UFI. Further large and randomized controlled trials for a promising clinical application of these general immunological evaluations in UFI are necessary.

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In brief

Immune system aberrations can interfere with normal embryo implantation and may lead to infertility. The authors illustrate that cases of unexplained female infertility (UFI) may have associated abnormalities in the total levels of immunoglobulins and/or complements. Additional management steps are necessary to address these abnormalities and their potential comorbidities.

Highlights:

- Healthy maternal immune system homeostasis is crucial for success conception and the delivery of normal fetuses.
- Several obstetrical guidelines are somewhat uncertain about the evidence for screening general immunological tests in cases of UFI.

- Total immunoglobulins and complements abnormalities may be detected in some cases of UFI.

References

1. Mol BW, Tjon-Kon-Fat R, Kamphuis E, van Wely M. Unexplained infertility: Is it over-diagnosed and over-treated? Best Pract Res Clin Obstet Gynaecol. 2018 Nov;53:20-29. doi: 10.1016/j.bpobgyn.2018.09.006.
2. Ehsani M, Mohammadnia-Afrouzi M, Mirzakhani M, Esmaeilzadeh S, Shahbazi M. Female Unexplained Infertility: A Disease with Imbalanced Adaptive Immunity. J Hum Reprod Sci. 2019 Oct-Dec;12(4):274-282. doi: 10.4103/jhrs.JHRS_30_19.
3. Brazdova A, Senechal H, Peltre G, Poncet P. Immune Aspects of Female Infertility. Int J Fertil Steril. 2016 Apr-Jun;10(1):1-10. doi: 10.22074/ijfs.2016.4762.
4. Castro C, Gourley M. Diagnostic testing and interpretation of tests for autoimmunity. J Allergy Clin Immunol. 2010 Feb;125(2 Suppl 2):S238-47. doi: 10.1016/j.jaci.2009.09.041.
5. Amino N, Tanizawa O, Miyai K, Tanaka F, Hayashi C, Kawashima M, Ichihara K. Changes of serum immunoglobulins IgG, IgA, IgM, and IgE during pregnancy. Obstet Gynecol. 1978 Oct;52 (4):415-20. PMID: 714321.
6. Zhang T, Hu Y, Xiang Z. Changes of serum immunoglobulin level in healthy pregnant women and establishment of its reference interval. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2021 Jan 28;46 (1):53-59. English, Chinese. doi: 10.11817/j.issn.1672-7347.2021.200468.
7. Girardi G, Lingo JJ, Fleming SD, Regal JF. Essential Role of Complement in Pregnancy: From Implantation to Parturition and Beyond. Front Immunol. 2020 Jul 31;11:1681. doi: 10.3389/fimmu.2020.01681.
8. Reichhardt MP, Lundin K, Lokki AI, Recher G, Vuoristo S, Katayama S, Tapanainen JS, Kere J, Meri S, Tuuri T. Complement in Human Pre-implantation Embryos: Attack and Defense. Front Immunol. 2019 Sep 18;10:2234. doi: 10.3389/fimmu.2019.02234. PMID: 31620138; PMCID: PMC6759579.
9. Jones CA, Hawkins L, Friedman C, Hitkari J, McMahon E, Born KB. Choosing Wisely Canada: Canadian fertility and andrology society's list of top items physicians and patients should question in fertility medicine. Arch Gynecol Obstet. 2022 Jul;306(1):267-275. doi: 10.1007/s00404-022-06453-z.
10. Vomstein K, Feil K, Strobel L, Aulitzky A, Hofer-Tollinger S, Kuon RJ, Toth B. Immunological Risk Factors in Recurrent Pregnancy Loss: Guidelines Versus Current State of the Art. J Clin Med. 2021 Feb 20;10(4):869. doi: 10.3390/jcm10040869.
11. Shaulov T, Sierra S, Sylvestre C. Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline. Reprod Biomed Online. 2020 Nov;41(5):819-833. doi: 10.1016/j.rbmo.2020.08.007. Epub 2020 Aug 20. PMID: 32962928.
12. Mascarenhas M, Jeve Y, Polanski L, Sharpe A, Yasmin E, Bhandari HM; British Fertility Society. Management of recurrent implantation failure: British Fertility Society policy and practice guideline. Hum Fertil (Camb). 2022 Dec;25(5):813-837. doi: 10.1080/14647273.2021.1905886. Epub 2021 Apr 5. PMID: 33820476.
13. Infertility world health organization international (who.int) 2023, https://www.who.int/news-room/

fact-sheets/detail/infertility

14. Deroux A, Dumestre-Perard C, Dunand-Faure C, Bouillet L, Hoffmann P. Female Infertility and Serum Auto-antibodies: a Systematic Review. Clin Rev Allergy Immunol. 2017 Aug;53(1):78-86. doi: 10.1007/s12016-016-8586-z. PMID: 27628237.
15. Ahmad HA, Salih MM, Khidir KA. Complement protein and Immunoglobulins Serum levels in Normal Pregnant and Spontaneous Aborted Women. Kurdistan Journal of Applied Research. 2018 Jul;3 (2):129-133. doi.org/10.24017/science.2018.2.21.
16. NHS Exeter Clinical Laboratory International. Immunoglobulins (IGA, IGG, IGM) (Accessed 13/6/2019). https://www.exeterlaboratory.com/test/immunoglobulins-iga-igg-igm/
17. Simopoulou M, Sfakianoudis K, Maziotis E, Grigoriadis S, Giannelou P, Rapani A, Tsioulou P, Pantou A, Kalampokas T, Vlahos N, Pantos K, Koutsilieris M. The Impact of Autoantibodies on IVF Treatment and Outcome: A Systematic Review. Int J Mol Sci. 2019 Feb 19;20(4):892. doi: 10.3390/ijms20040892. PMID: 30791371; PMCID: PMC6412530.
18. Gleicher N, Liu HC, Dudkiewicz A, Rosenwaks Z, Kaberlein G, Pratt D, Karande V. Autoantibody profiles and immunoglobulin levels as predictors of in vitro fertilization success. Am J Obstet Gynecol. 1994 Apr;170(4):1145-9. doi: 10.1016/s0002-9378(94)70110-5. PMID: 8166199.
19. Sugiura-Ogasawara M, Nozawa K, Nakanishi T, Hattori Y, Ozaki Y. Complement as a predictor of further miscarriage in couples with recurrent miscarriages. Hum Reprod. 2006 Oct;21(10):2711-4. doi: 10.1093/humrep/del229.
20. Wilson R, Maclean MA, Jenkins C, Kinnane D, Mooney J, Walker JJ. Abnormal immunoglobulin subclass patterns in women with a history of recurrent miscarriage. Fertil Steril. 2001 Nov;76(5):915-7. doi: 10.1016/s0015-0282(01)02857-6.
21. Zhang XY, Li JJ. Effect of complement C3 and C4 in the pathogenesis of recurrent spontaneous abortion. Journal of Dalian Medical University. 2011 August,33(4):353-356.
22. Cowchock S, Dehoratius RD, Wapner RJ, Jackson LG. Subclinical autoimmune disease and unexplained abortion. Am J Obstet Gynecol. 1984 Oct 15;150(4):367-71. doi: 10.1016/s0002-9378(84)80140-4. PMID: 6333181.
23. Unander AM, Norberg R, Hahn L, Arfors L. Anticardiolipin antibodies and complement in ninety-nine women with habitual abortion. Am J Obstet Gynecol. 1987 Jan;156(1):114-9. doi: 10.1016/0002-9378(87)90218-3.
24. Micheloud D, Sarmiento E, Teijeiro R, Jensen J, Rodríguez Molina JJ, Fernández-Cruz E, Carbone J. Hypocomplementemia in the absence of autoantibodies in women with recurrent pregnancy loss. Allergol Immunopathol (Madr). 2007 May-Jun;35(3):90-4. doi: 10.1157/13106775.
25. Al-Khyat Z, Waheda N, Shaker N. Complement C3 and C4 Levels in Recurrent Aborting Women with or without Antiphospholipid and Anticardiolipin Autoantibodies. Ibnosina Journal of Medicine and Biomedical Sciences . 2014 September;6(5):213-218. doi.org/10.4103/1947-489X.210388.