Sarcouncil journal of Medical sciences

ISSN(Online): 2945-3526

Volume- 03| Issue- 05| 2024

Research Article **Received:** 28-03-2024 | **Accepted:** 27-04-2024 | **Published:** 29-05-2024

Immune System Disorders on Women's Fertility and Identifying Risk Factors

Dr. Halah Abdul Wahab Mohammed[1], Dr. Afrah Naser kadhim Almusawi[2] and Dr. Rawya Mansoor Abdullah[3]

[1]M.B.Ch.B., D.G.O., C.A.B.O.G. \ (Obstetrics & Gynecology) Specialist Obesterics and Gynogology Iraqi Ministry of Health, Baghdad, Iraq.

[2]M.B.Ch.B., D.G.O., C.A.B.O.G. \ (Obstetrics & Gynecology) Specialist Obesterics and Gynogology Iraqi Ministry of Health, Baghdad Medical office Al-Karkh, Al-Karama Teaching Hospital, Baghdad, Iraq.

[3]M.B.Ch.B., D.G.O., C.A.B.O.G. \ (Obstetrics & Gynecology) Specialist Obesterics and Gynogology Iraqi Ministry of Health, Baghdad Medical office Al-Karkh, Al-Karama Teaching Hospital, Baghdad, Iraq

Abstract: A cross-sectional study was conducted in different hospitals in Iraq, involving 110 cases from various hospitals, with the objective of diagnosing autoimmune disorders and their impact on fertility in Iraqi women from March 2023 to February 2024. The study employed a descriptive approach to assess the impact of treatment on women and identify any negative effects after pregnancy. A questionnaire comprising 50 items was distributed to patients, covering personal information, primary immunodeficiency diseases, family experiences, perceptions of fertility and childbirth, and the influence of immunodeficiency on pregnancy -decisions. Data was analysed using Microsoft Excel, Microsoft Access, and SPSS. A higher prevalence of autoimmune diseases is noted among women compared to men, with more than 85% of all patients suffering from multiple such conditions being female. Women experience two intense endocrine changes in their lives: puberty and menopause. Most women also go through a transition period, possibly involving pregnancy or breastfeeding that sometimes lasts months or years. The immune system changes by the endocrine are important to modifying vulnerability in women, as these changes involve numerous hormonal milieu interactions and their pathways between the innate and acquired immune response mechanisms. So, human resistivity to autoimmune diseases is altered. Again, certain pre-existing autoimmune conditions can also alter them. It affects the immunity system by estrogen-dependent concentration.

Keywords: Immune system, Endocrine, Estrogen, Fertility, Women, Hormonal, Diseases.

INTRODUCTION

The recognition of infertility as a global health problem is increasing at an exponential rate. Despite the remarkable scientific and technological developments achieved in the field of reproductive biology, the number of couples seeking medical advice and infertility treatment is increasing significantly (ojas-Villarraga, A. *et al.*, 2010).

Autoimmune diseases are a group of conditions in which the body's immune system attacks healthy cells and tissues, considering them foreign or abnormal. Instead of attacking any harmful foreign bodies, the immune system begins to attack healthy tissues by forming antibodies against them.

The perception that infertility is becoming increasingly prevalent is not without foundation. Indeed, the risk of infertility also increases as an increasing number of couples choose to delay childbearing until they are older and statistically less fertile. Nevertheless, this reproductive disorder can occur at any time, during the fertile age of a man or a woman. The global prevalence of infertility is estimated to range between 3.5 to 16.7% in developed countries and between 6.9 to 9.3% in less developed countries. According to studies, the prevalence of this clinical entity ranges from 12 to 14%. 6-8 (McCarthy, Michael., 2000; Petri, Michelle., 1995; Walsh, Stephen J., and Laurie M. Rau., 2000).

It is well-established that autoimmune conditions can have a significant impact on fertility in both women and men. The immune system plays a crucial role in maintaining the optimal functioning of the body, including the reproductive organs (Rees, F. *et al.*, 2016; van Vollenhoven, Ronald F., 2009; Thierry, S. *et al.*, 2014).

The immune system is responsible for stimulating the formation and development of the placenta by stimulating the growth of certain blood vessels. In the event that the risk of infection and disease increases, a compromised immune system may be unable to support the pregnancy (Magyari, Melinda., 2009; Maahs, D. M. *et al.*, 2010).

Despite recent advances in the diagnosis and monitoring of infertility, the causes of infertility remain undetermined in between 10 and 20% of cases. 3.6 These unknowns in the study of infertility present a challenge for medical science and, thus, are not considered an exclusive legacy of obstetrics and gynaecology. Rather, they require various evaluations by other trained specialists (Reimand, K. *et al.*, 2000; Uibo, R. *et al.*, 1994; Edassery, S. L. *et al.*, 2010). A recent study has indicated a strong correlation between fertility disorders and functional changes in the immune system, which contribute to the origin and maintenance of infertility (Harris, P. A. *et al.*,

***Corresponding Author:** Dr. Halah Abdul Wahab Mohammed

DOI-https://doi.org/10.5281/zenodo.11379268

2009).The field of reproductive immunity has gained significant interest in recent times, primarily due to the necessity to identify a treatable cause of idiopathic infertility. Secondly, there is a clear advantage to be gained from the development of a highly specific method of contraception by vaccinating individuals against pregnancy.

MATERIAL AND METHOD

Collection Data

A cross-sectional study was conducted in different hospitals in Iraq, with samples collected from several different hospitals. A total of 110 cases were collected for the purpose of diagnosing autoimmune disorders and their impact on fertility in Iraqi women. The time period for the preparation and analysis of the results of this study was one year, from 1 March 2023 to 7 February 2024.

Study design

This study was designed according to the descriptive approach, with the distribution of a questionnaire to patients. The objective was to ascertain the effect of the treatment on women, as well as to identify any negative effects that may have occurred following pregnancy. In addition, the quality of life measure was employed to gauge the psychological impact on women.

A comprehensive questionnaire comprising 50 items was devised with the intention of eliciting responses pertaining to a range of domains. These included personal information, details of primary immunodeficiency diseases affecting the self and relatives, general information about diseases experienced by immediate family members, as well as rare conditions, perceptions regarding fertility and childbirth, and the influence of immunodeficiency on child-rearing decisions.

We collected and analyzed all survey responses using Microsoft Excel, Microsoft Access, and SPSS statistical software (IBM Corporation) in aggregate to carry out descriptive statistics together with a chi-square test comparison between fertility measured as the percentage of respondents who had given birth.

Aim of study

This study aimed to identify immune system disorders in women's fertility and identify risk factors.

RESULTS

Table 1- General demographic of patients

Parameter	**P%**	**f**
Age, f (%)		
25-29	27,27	30
30-34	45,45	50
35-40	27,27	30
BMI f (%)		
25-28	22,73	25
29-31	40,91	45
>31	36,36	40
Comorbidities f (%)		
blood pressure	26,36	29
Kidney diabetes	19,09	21
Migraines	27,27	30
others	27,27	30
Self-reported diagnosis f (%)		
CVID	90,91	100
Hypogammaglobinemia	9,09	10
Receive alternative treatment f (%)		
YES	72,73	80
NO	27,27	30
Type of Receive alternative treatment f (%)		
Intravenous route	45,45	50
Subcutaneous route	20,00	22
Intramuscular route	25,45	28

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Intravenous and subcutaneous	9,09	10
Outcomes f (%)		
400-800$	50,00	55
900-1200$	31,82	35
>1200$	18,18	20
Education f (%)		
Primary	10,00	11
Secondary	26,36	29
College	54,55	60
High	9,09	10

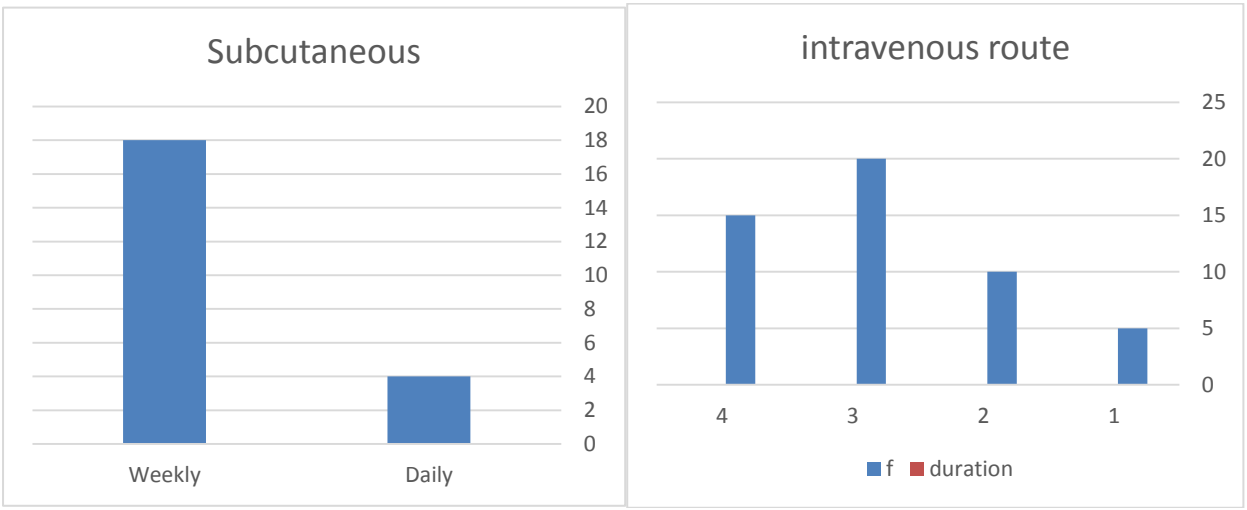

Fig 1- The time period depends on the frequency of alternative treatment by week. Repeat IgG replacement therapy.

Table 2- Evaluation of medical conditions according to the survey conducted on relatives on the diagnosis of immunodeficiency

	Mother	Father	Brother n= (51)	Sister, N=40
presence of thyroid disorders	12	16	4	7
asthma	20	18	16	4
Rheumatism	21	25	15	11
Hypertension	39	35	10	10
Heart disease	18	16	6	8

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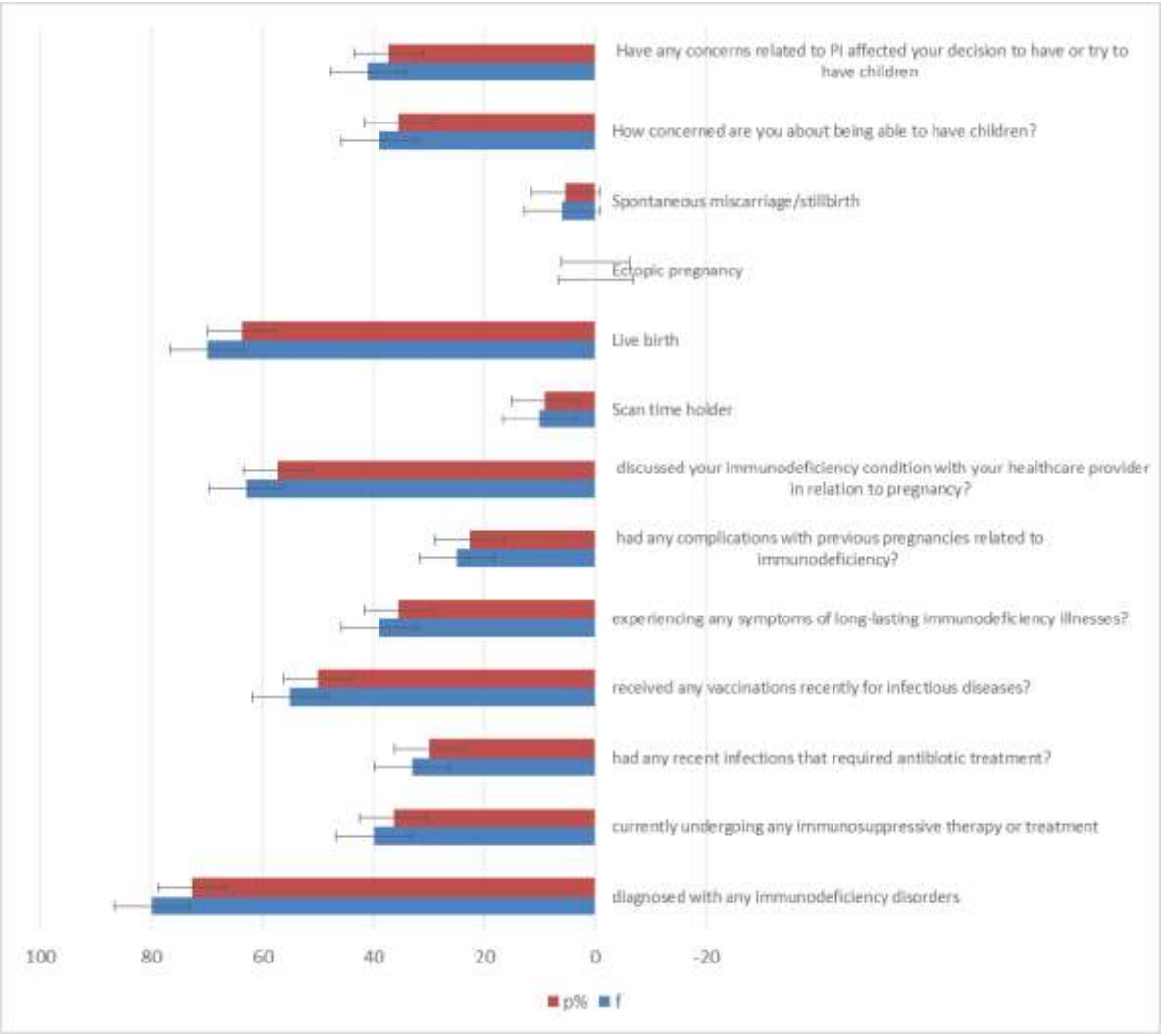

Fig 2- Health outcomes for patients according to a questionnaire to know patients' comments and its impact on pregnancy

Table 3- Study results of lifestyle behaviors regarding infertility in Iraq.

Variable	Mean	SD
Anxiety	63	11
Depression	45	4.7
Social side	55.7	5.9
Psychological factor	50.2	5.4

Table 4- Final outcomes related with Immune system disorders on women's fertility

Live birth rate, n (%)	55 (50)
Clinical pregnancy, n (%)	33 (30)
Twin pregnancy, n (%)	4 (3.6)
Triplets, n (%)	-
Ectopic pregnancy, n (%)	2 (1.82)
Pregnancy loss, n (%)	15 (13.6)

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Table 5- Logistic regression analysis of patients to determine the risk factors affecting this study

Variable	95% CI	Adjusted Risk Ratio	P value
Age			
35-40	2.88-3.77	3.1	<0.001
Smoking	1.4-1.8	1.6	0.04
Anxiety	1.55-3.1	2.44	<0.001
Depression	1.9-2.8	1.7	0.08
IgG	0.99–1.36	1.1	0.89
Outcomes	2.4-4.3	3.2	<0.001
Pregnancy loss	2.6-3.7	3.18	0.0023
Past medical history	1.76-2.65	2.13	<0.001
Pregnancy Third trimester	2.5-2.98	2.76	0.00

DISCUSSION

The results of experimental studies on animals indicate that the loss of immune tolerance in the female reproductive system is determined by the influence of estrogens. These hormones exert a direct influence on the primary process of physiological elimination of self-reactive lymphocytes, which appear in primary and secondary lymphoid organs. The involvement of IL-17-secreting helper T lymphocytes has been proposed as a potential basis for uncontrolled inflammation in certain endocrinopathies. Nevertheless, its role in reproductive disorders remains to be fully elucidated (Elbakry, S. A. *et al.*, 2020).

A reduction in fertility can be attributed to factors affecting the fallopian tubes, including defects in oocyte transfer and/or adnexal adhesion. Among the potential causes of these abnormalities in the tubes are infections, pelvic surgeries, and endometriosis. In all of these cases, the degree of tubal injury is dependent on the degree of tissue damage that is achieved once the autoimmune inflammatory response is activated. It has recently been observed that in the event of infection, the production of heat shock proteins is significantly increased (Cigni, A. *et al.*, 2008).These proteins share structural homology with microbial amino acid sequences, which generates cross-reactivity and makes them a target for the autoreactive response after the pathogen is eliminated(Huang, C. *et al.*, 2020).

Although it is commonly assumed that autoimmune diseases have a profound impact on female fertility, it is important to note that each of the more than 80 known autoimmune disorders exhibits distinct characteristics with regard to fertility. Although it is true that approximately 20% of cases of unexplained infertility are typically attributable to some form of immune disorder, previous studies pertinent to the present study indicate that autoimmune diseases exert a significant influence on female fertility (Huang, C. *et al.*, 2020; Elshafeey, F. *et al.*, 2020; Murad, M. H. *et al.*, 2018). Among the more than 80 autoimmune disorders that have been identified, each has distinctive characteristics with regard to fertility. Although it is true that approximately 20% of cases of unexplained infertility are typically attributable to some form of immune disorder .

Nevertheless, in the event of underlying diseases, such as disorders of an immune origin, the female body may perceive sperm or the fetus as foreign agents, thereby leading to conditions defined as immunological infertility (Monteleone, P. *et al.*, 2011).

Among the various forms of lupus, the most frequently associated with female infertility is SLE. This systemic autoimmune disease is characterized by inflammation and tissue damage and can affect any part of the body. However, the reproductive system is one of the most common areas affected (Poppe, K., & Velkeniers, B. 2002).

Nevertheless, women diagnosed with this disease are not necessarily infertile. Indeed, scientific advances have enabled numerous women with SLE to become pregnant and to continue their pregnancies to term. While it is true that pregnancies must be highly planned, often accompanied by assisted reproductive techniques to carefully control aspects such as medications and number of attempts, there can still be more complications associated with pregnancy, such as decreased ovarian reserve dysfunction. Furthermore, irregular menstruation, including the loss of the pregnancy itself, may also occur.

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It can be reasonably deduced that the key to a successful pregnancy is to have no disease activity in the last six months and to use a treatment that does not promote flare-ups. This is because some nonsteroidal anti-inflammatory drugs used to combat SLE can cause complications during pregnancy and spontaneous abortion, as can some corticosteroids. Furthermore, immunosuppressants should be avoided.

Autoimmune diseases are typically diagnosed in women of childbearing age. While some autoimmune diseases, such as rheumatic diseases, can cause vaginal dryness, changes in the menstrual cycle, and pain during intercourse, these symptoms are not indicative of decreased fertility.

Autoimmune diseases have a significant hormonal effect. Since pregnancy involves major hormonal changes, combining the two can cause complications.

The hormonal status of pregnancy can result in the disease being either remitted or reduced in its harmful consequences. However, this protective effect is reduced when the baby is born, and the disease can be reactivated more strongly, causing outbreaks or relapses also. Genetic factors have been identified as a significant contributor to reproductive disorders, affecting both men and women. Some causes exhibit a well-defined pattern of purely genetic changes, whereas others involve the involvement of multiple genes.
A number of genetic alterations can impact female reproductive function, including mutations in the X chromosome, as well as mutations in sex steroid hormones, adrenal steroids, and nuclear hormone receptors.

In studies of fertility disorders, cytogenetic studies should be performed. Chromosomal abnormalities are observed in approximately 1 in 500 individuals in the general population. Studies of infertile or infertile individuals have revealed marked differences in the frequency of chromosomal aberrations. This discrepancy may be attributed to disparate selection criteria for cytogenetic studies, varying degrees of control over environmental variables, such as infections, and the timing of the studies in these individuals.

CONCLUSION

The diagnosis of infertility, whether gynecological, endocrine, immunological, or genetic, does not exempt infertile couples from a comprehensive evaluation in the study. In light of the aforementioned considerations, it can be posited that studies of couples suffering from reproductive disorders must be conducted by a multidisciplinary medical team with the objective of elucidating the etiology, diagnosis, and provision of appropriate reproductive options.

Female fertility can be affected by a number of different diseases or dysfunctions, including those affecting the reproductive system, neuroendocrine system, and immune system. Reproductive autoimmune failure may be associated with systemic activation of the immune system or with immune system reactions specifically directed against ovarian antigens.

The aforementioned studies indicate that the use of IgG replacement during pregnancy has yielded positive results without the occurrence of any adverse events. This survey output can serve as a source of peer support for patients. Moreover, these outcomes should provide a framework within which more effective counselling protocols can be established regarding these important and worrying areas.

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Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Mohammed, H.A.W., Almusawi, A.N.K. and Abdullah, R.M. "Immune System Disorders on Women's Fertility and Identifying Risk Factors." *Sarcouncil journal of Medical sciences* 3.5 (2024): pp 41-47.

Publisher: SARC Publisher