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Does autoimmune disease affect in vitro fertilization results in normo-responder cases?

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ABSTRACT

Aims: This study aimed to assess the effects of autoimmune disorders on pregnancy outcomes in infertile women undergoing in vitro fertilization (IVF) treatment.

Methods: This retrospective cohort study was conducted between March 2022 and September 2023, involving 90 infertile women without autoimmune diseases as a control group and 96 infertile women with autoimmune diseases as a case group. The study investigated the impact of autoimmune diseases on IVF treatment outcomes. Single embryo transfer (ET) was performed on the fifth day in all patients. Autoimmune diseases included in this study as Hashimoto's disease, Rheumatoid Arthritis, Sjogren's syndrome, Systemic lupus erythematosus (SLE), Ulcerative Colitis, and Behcet's disease.

Results: There was no statistically significant association between the case and control groups regarding live birth rate ($p>0.05$). Similarly, no statistically significant association was found between the case and control groups concerning the clinical pregnancy rate ($p>0.05$). Our results revealed that total oocyte, pronuclear (PN), and metaphase II (MII) oocyte rates were statistically significantly higher in healthy infertile women ($p<0.05$). The number of attempts, anti mullerian (AMH) levels, total gonadotropin dose, and total days were similar between the groups ($p>0.05$).

Conclusion: Autoimmune diseases do not significantly affect pregnancy outcomes in women undergoing IVF. However, several factors, such as total oocyte, PN, and MII oocytes, clinical pregnancy rate (CPR), and live birth rate (LBR) levels, support the association between autoimmune diseases and IVF outcomes.

Keywords: Autoimmune disease, clinical pregnancy rate, in vitro fertilization, pregnancy outcomes, infertility

INTRODUCTION

Infertility is defined as the inability to achieve pregnancy after one year of unprotected and regular sexual relations.[1] Assisted reproductive technology (ART) has served as a solution to the problem of infertility since 1978.[2,3] Over the past few decades, ART has expanded and undergone significant improvements.[4,5] Despite the millions of recorded live births through ART, there remain numerous frustrated couples experiencing failed attempts.[6] The likelihood of successful live birth with in vitro fertilization (IVF) is contingent on various factors, including maternal age and the underlying cause of infertility.[7] The identification of factors influencing the success rate of IVF remains a contentious issue in obstetrics and gynecology studies.[8,9]

An autoimmune disease is characterized by the aberrant functioning of an individual's immune system, wherein the body produces antibodies that mistakenly target and attack its own tissues.[10] Cases of autoimmune diseases predominantly occur in youth and middle age, affecting at least 7% of individuals and exhibiting a higher prevalence in women than men.[11,12] In the early years of recognizing autoimmune diseases, it was advised that affected women should avoid pregnancy.[13] Scholars have posited that autoimmune diseases may exacerbate during pregnancy, potentially leading to adverse consequences for both the mother and the fetus.[13,14] Over time, substantial information has been gathered regarding the impact of various autoimmune diseases on pregnancy outcomes and the potential exacerbation of the mother's condition during pregnancy.[15] In the last 20 years, the management of these diseases during pregnancy and the overall quality of life for patients have undergone positive changes.[16]

The immune system plays a crucial role in the process of fertilization and the maintenance of pregnancy.[17] As half of

the fetus originates from the father, it is perceived as a foreign entity by the mother's body, prompting a response from her immune system. In a successful pregnancy, the mother's immune system undergoes adaptation to recognize, accept, and tolerate the developing fetus.[1] However, if the mother's immune system is compromised due to autoimmune diseases, it may struggle to adapt to the fetus. In such situations, there is a risk of preventing the embryo's implantation, ultimately leading to abortion.

This study explored the association between autoimmune diseases, such as Hashimoto's and Rheumatoid Arthritis, and the outcomes of IVF treatment. The primary objective was to investigate whether autoimmune diseases are linked to pregnancy outcomes following IVF treatment. Another aim was to determine whether these diseases should be routinely taken into account in the management of infertile women undergoing IVF.

METHODS

This retrospective study was conducted on infertile women between March 2022 and September 2023. Approval from the local ethics committee was obtained from Bezmialem Vakıf University Hospital Ethics Committee (Date: 06.11.2023; Decision No: 2023/291). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion criteria comprised infertile women of reproductive age (20-45 years) with primary or secondary infertility and those undergoing their first cycle of IVF. Exclusion criteria encompassed repeated pregnancy loss, ovarian hyperstimulation syndrome, chronic diseases, cardiovascular problems, endocrine diseases, infertility attributed to severe endometriosis, and uterine abnormalities.

Autoimmune diseases included in this study as Hashimoto's disease, Rheumatoid Arthritis, Sjogren's syndrome, Systemic lupus erythematosus (SLE), Ulcerative Colitis, and Behcet's disease. The case group comprised 96 infertile women with autoimmune diseases, while the control group consisted of 90 infertile women without any diseases.

IVF pregnancy is achieved through the following stages: egg collection, retrieval of a sperm sample, fertilization, embryo culture, and subsequent transfer of a fresh or frozen blastocyst to the uterus. A single embryo transfer was conducted on the fifth day for all patients. Parameters such as the number of attempts, anti mullerian hormone (AMH) levels, total gonadotropin dose, total days, total oocytes, fertilization-ready metaphase II (MII) oocytes, pronuclear (PN) status, and the number of cryopreserved embryos were measured in both the case and control groups.

Statistical Analyses

The normality of the quantitative data was assessed using the Kolmogorov-Smirnov test and histogram graphs. Upon reviewing the normality test results, a Mann–Whitney U test was employed to compare numerical parameter values between groups. Descriptive statistics for the data were reported using Median (M) and Interquartile Range (IQR). Categorical variables were described in terms of number and percentage and analyzed using a Chi-square test. Statistical analysis was performed using SAS statistical software, with the threshold for statistical significance set at a p-value of less than 0.05.

The G-Power 3.2 program was utilized to estimate the sample size. The calculation for the difference between two independent proportions was conducted using a Mann–Whitney U test with a power of 80%, effect size of 50%, and a type 1 error of 0.05, requiring a minimum of 146 patients.18

RESULTS

This investigation included one hundred eighty-six age-matched (32, range: 30.75-36) and body mass index (BMI)-matched (24, range: 23-25) infertile women. Table 1 provides a statistical description of age, BMI, number of attempts, AMH, total gonadotropin dose, total days, total oocytes, MII oocytes, PN status, the number of cryopreserved embryos, clinical pregnancy rate (CPR), and live birth rate (LBR).

As depicted in **Table 1**, the frequency of autoimmune diseases in the current study is as follows: Hashimoto (85.5%), Rheumatoid Arthritis (5.3%), Sjogren's syndrome (2%), SLE (3.2%), Ulcerative Colitis (2%), and Behcet (2%).

Table 1. Statistical description of study parameters in infertile women (n=186)

Study parameters	Median (IQR) or n (%)
Age (years)	32 (30.75-36)
BMI (kg/m²)	24 (23-25)
Number of attempts	1 (0-2.25)
AMH (ng/ml)	1.40 (1.3-1.6)
Total gonadotropin dose	2250 (2000-2250)
Total days	10 (9-11)
Total Oocyte	10 (8.75-11)
MII	9 (8-9)
PN	9 (8-9)
The number of cryopreserved embryos	2 (2-2)
Clinical pregnancy test results	
Positive	110 (59.1)
Negative	76 (40.9)
Live birth	
Yes	99 (53.2)
No	11 (5.9)
The autoimmune disease frequency	
Hashimoto	82 (85.5)
Rheumatoid Arthritis	5 (5.3)
Sjogren's syndrome	2 (2)
SLE	3 (3.2)
Ulcerative Colitis	2 (2)
Behcet	2 (2)

SD, standard deviation; n, number; BMI, body mass index; AMH, anti Mullerian hormone, MII, metaphase II; PN, pronuclear; SLE, systemic lupus erythematosus

As shown in **Table 2**, the Mann–Whitney U test did not identify a statistically significant difference between normo-responder women with autoimmune diseases and healthy women in terms of age and BMI (p>0.05). There was no statistically significant difference between infertile women with autoimmune diseases and the control group regarding AMH levels (p>0.05). The median and interquartile range of AMH levels in the case and control groups were 1.4 (1.3-1.6) and 1.4 (1.3-1.52), respectively. The number of attempts,

AMH, total gonadotropin dose, total days, and the number of cryopreserved embryos were similar in the two groups (p>0.05). However, total oocytes, MII oocytes, and PN status were significantly higher in the control group (p<0.05).

As presented in **Table 2**, the chi-squared test did not identify a statistically significant difference between normo-responder patients with autoimmune diseases and healthy women in terms of CPR (p>0.05). The CPR in the groups with autoimmune diseases and the healthy groups were 53 (55.2%) and 57 (63.3%), respectively.

Similarly, as indicated in **Table 2**, the chi-squared test did not find a statistically significant difference between normo-responder women with autoimmune diseases and healthy women in terms of LBR (p>0.05). The LBR in the groups with autoimmune diseases and the healthy groups were 46 (47.9%) and 53 (58.9%), respectively.

Table 2. Comparison of the normo-responder women with autoimmune diseases and healthy groups

Study parameters	Case group (n=96) Median (IQR) n (%)	Healthy group (n=90) Median (IQR) n (%)	p-value
Age (years)	31 (30-36)	33 (31-36.25)	0.162*
BMI (kg/m²)	24 (22.25-25)	24 (23-25)	0.720*
Number of attempts	1 (0-2)	1 (0-3)	0.738*
AMH	1.4 (1.3-1.6)	1.4 (1.3-1.52)	0.833*
Total gonadotropin dose	2250 (2000-2250)	2250 (2000-2250)	0.876*
Total days	10 (9-11)	10 (9-11)	0.821*
Total oocyte	9 (8-10)	10 (9-11)	0.001*
MII oocytes rate	8 (8-9)	9 (8-10)	<0.001*
PN	8 (8-9)	9 (8-9.25)	<0.001*
The number of cryopreserved embryos	2 (2-2)	2 (2-2)	0.12*
Clinical pregnancy			0.260**
Positive	53 (55.2)	57 (63.3)	
Negative	43 (44.8)	33 (36.7)	
Live births			0.296**
Yes	46 (47.9)	53 (58.9)	
No	50 (52.1)	37 (41.1)	

* A Mann–Whitney U test **A chi-squared test. n, number; BMI, body mass index; AMH, anti Mullerian hormone, MII, metaphase II; PN, pronuclear; SLE, systemic lupus erythematosus

In **Figure 1**, the bar chart depicts the number of positive clinical pregnancies and the live birth rate between infertile women with autoimmune diseases and healthy groups. It is evident that the CPR decreased slightly from 63.3% to 55.2% in women with autoimmune diseases. The LBR is relatively lower in women with autoimmune diseases compared to healthy women (47.9% vs. 58.9%).

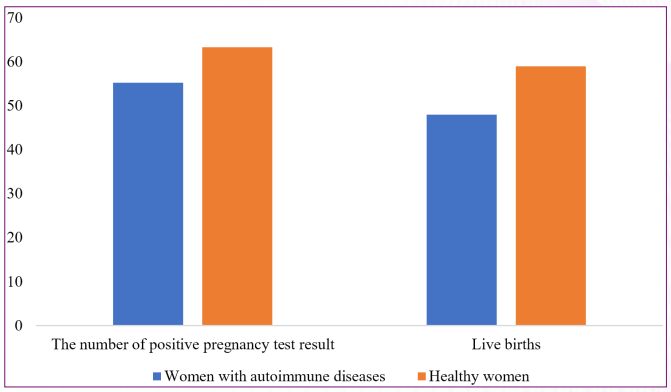

Figure 1. Comparison of CPR and LBR between groups

DISCUSSION

In our study, CPR and LBR were relatively higher in healthy women; however, this difference was not statistically significant. The autoimmune diseases + group exhibited a significantly lower rate of MII oocytes, PN status, and total oocytes. In this study, autoimmune diseases had no significant effect on IVF treatment outcomes.

The production of various antibodies can lead to immune system disorders. Previous studies have explored the impact of these antibodies on implantation failure and IVF treatment outcomes, yielding contradictory results. Antinuclear antibodies (ANA) target normal proteins in the nucleus of the body's cells and may indicate autoimmune diseases such as dermatomyositis, scleroderma, SLE, rheumatoid arthritis, and Sjögren's syndrome.[19]

Berestoviy et al.[20] reported that antiphospholipid, antithyroid, and ANA in recipients of oocyte donations did not affect their pregnancy results. Chen et al.[21] in a prospective cohort study with 3763 women, found no association between ANA, anti-thyroperoxidase, and antithyroglobulin antibodies and IVF/ intracytoplasmic sperm injection (ICSI) outcomes, aligning with our results. Li et al.[22] in a case-control study with 380 women, observed an association between ANA and poor IVF-ET treatment outcomes. Li et al.[23] suggested that ANA positivity might pose a risk factor for IVF/ICSI treatment but may not be the sole reason for poor outcomes.

Contrastingly, Zhu et al.[24] reported adverse effects of ANA on IVF-ET treatment outcomes and recommended prednisone plus low-dose aspirin adjuvant treatment to increase the implantation rate in IVF-ET. Ying et al.[25] highlighted the detrimental impact of ANA in follicular fluid on IVF outcomes. These studies present varying results compared to the current study.

Ticconi et al.[26] in a comprehensive meta-analysis and systematic review, investigated the potential relationship between ANA and IVF treatment outcomes and pregnancy complications. They reported lower implantation and pregnancy rates among ANA-positive women compared to healthy women, suggesting that ANA may have a detrimental effect on IVF results. However, in some studies, such as the results of the present study, this effect may not reach statistical significance.

Thyroid autoimmunity occurs when the body produces antibodies that target the cells in the thyroid. The detrimental impact of these antibodies on ART results has been reported in previous studies.[27] However, in recent years, there has been no consistent relationship between this condition and IVF outcomes, and the findings are conflicting.

Weghofer et al.[28] demonstrated that thyroid autoimmunity has a negative effect on live births and CPR results in IVF treatment outcomes. In contrast, Busnelli et al.[27] found that thyroid autoimmune disease does not influence implantation and clinical pregnancy rates, although live births and the risk of miscarriage increased in women with thyroid autoimmune disease. A large retrospective cohort study by Bliddal et al.[29]

reported that thyroid autoimmunity in infertile euthyroid women was not associated with LBR or embryo quality. Rao et al.[30] reported that thyroid autoimmunity in women was not linked to live births or embryo quality following IVF/ICSI. Similarly, the retrospective cohort study by Hamad et al.[31] showed that thyroid autoimmune disease did not adversely affect CPR.

In summary, the current study suggests no detrimental impact of autoimmune diseases such as Hashimoto and Rheumatoid Arthritis on IVF outcomes in Turkish infertile women. However, certain factors, including CPR and LBR levels, lean towards a potential association between autoimmune diseases and IVF/ICSI outcomes. The findings reveal relatively higher CPR and LBR in healthy women. The apparent absence of a significant relationship between autoimmune disorders and pregnancy outcomes suggests that testing for autoimmune diseases may not be necessary for women undergoing their first IVF treatment.

Nevertheless, further investigation with a larger sample size and randomized controlled trials is necessary to substantiate the potential impact of autoimmune diseases on IVF results. Additional studies involving normal pregnant women are also essential to comprehensively understand the relationship between autoimmune diseases and infertility. These results have reignited the discussion, prompting scientists to conduct more substantial investigations to gain deeper insights into the matter.

Limitations

The current study has several limitations. Firstly, the study size is small, and data were collected from a single center, underscoring the need for future studies with larger participant pools and conducted across multiple centers. While the study investigated the impact of autoimmune diseases on the female reproductive system of infertile Turkish women, it is recommended that future research explore each autoimmune disease separately. This approach would allow for a more detailed and accurate examination of their respective effects on IVF treatment outcomes.

CONCLUSION

The findings of the current study suggest that autoimmune diseases do not have a significant impact on pregnancy outcomes in women undergoing IVF. However, certain indicators, such as CPR and LBR levels, somewhat support a potential association between autoimmune diseases and IVF/ICSI outcomes. While CPR and LBR were relatively higher in healthy women, the differences were not statistically significant. The results of this investigation may offer valuable insights when formulating treatment programs for women undergoing IVF. Nonetheless, further studies are crucial to enhance our understanding of the effects of autoimmune diseases on the success rate of IVF.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bezmialem Vakıf University Hospital Ethics Committee (Date:06.11.2023; Decision No:2023/291).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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