RESEARCH ARTICLE

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Geliş tarihi / *Received* : September 03, 2024
Kabul Tarihi / *Accepted* : October 20, 2024

Cite this article as
Bu makalede yapılacak atıf
Alkan Bulbul G, Kirtis E, Ceylan SM, Olgan S, Ozekinci M, Sanhal CY, Mendilcioglu II. In Vitro Fertilization in 60 Women with Auto-inflammatory or Uncommon Autoimmune Diseases: A Single-Center Experience

Akd Med J 2025;11(3): 396-403

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In Vitro Fertilization in 60 Women with Auto-inflammatory or Uncommon Autoimmune Diseases: A Single-Center Experience

Otoinflamatuar veya Otoimmün Hastalıkları Olan 60 Kadında İn Vitro Fertilizasyon: Tek Merkez Deneyimi

ABSTRACT

Objective

Autoimmune and auto-inflammatory diseases can affect both the timing and ability of women to conceive. There is limited data addressing the outcomes of in vitro fertilisation (IVF) in autoimmune and auto-inflammatory-related infertility. This study presents the IVF experience in women diagnosed with at least one auto-inflammatory disease or autoimmune disorder except for the more common autoimmune disorders that primarily impact the thyroid gland.

Material and Methods

A retrospective analysis was performed on women diagnosed with at least one autoimmune or auto-inflammatory disease and had undergone at least one IVF cycle between 2014 and 2023.

Results

The study included 60 women who underwent a total of 74 IVF procedures. Rheumatoid arthritis was the most common autoimmune condition, affecting 26.6% of the patients, closely followed by Familial Mediterranean Fever (FMF) in 25% of the patients. The main factor causing infertility in the sample population was the diminished ovarian reserve, which affected around 64.9% of the participants. The median age at the time of IVF was 33 years. Out of 74 IVF cycles, there were 15 pregnancies, resulting in 9 live births (60%) and 6 miscarriages (40%). The IVF clinical pregnancy rate was 20.2% and the live birth rate was 12.1%. Obstetric complications included one case each of preterm birth, preeclampsia, and fetal growth restriction. No maternal or neonatal deaths occurred, and no cases of ovarian hyperstimulation syndrome were reported.

Conclusion

The outcomes of IVF in 60 patients diagnosed with autoimmune and auto-inflammatory diseases were analysed in this study. The IVF procedure exhibited comparatively low pregnancy and live birth rates. However, more than half of the on-going pregnancies resulted in live births. IVF remains a promising option for fertility treatment in patients with autoimmune diseases.

Key Words

Autoimmune, Auto-inflammatory, In-vitro fertilization, Infertility, Pregnancy

DOI: 10.53394/akd.1539790

ÖZ

Amaç

Otoimmün ve otoinflamatuar hastalıklar, kadınların gebe kalma zamanlamasını ve yeteneğini geciktirebilmektedir. Bugüne kadar, otoimmün ve otoinflamatuar hastalıklar ile ilişkili infertilitede İn Vitro Fertilizasyonun (IVF) sonuçlarına ilişkin çok az veri mevcuttur. Mevcut çalışmada, en sık görülen tiroid bezine karşı otoimmün hastalıklar dışında otoimmün hastalıklardan veya otoinflamatuar hastalıklardan en az birine sahip kadınlarda IVF deneyimini bildirdik.

Gereç ve Yöntemler

En az bir otoimmün veya otoinflamatuar hastalığı olan ve 2014 ile 2023 yılları arasında en az bir IVF prosedürü geçirmiş kadınlar üzerinde retrospektif bir analiz yapıldı.

Bulgular

Çalışmaya toplam 74 IVF uygulanan 60 kadın dahil edildi. Hastaların %26,6' sını etkileyerek romatoid artrit en sık karşılaşılan otoimmün hastalık olup bunu %25 ile Ailesel Akdeniz Ateşi izledi. Azalmış overyan rezervi infertilitenin birincil nedeniydi ve örnek popülasyonun %64,9'unu etkiledi. IVF sırasındaki ortalama yaş 33 idi. Yetmişdört IVF siklusunun 15'inde gebelik elde edildi, bunun 9'u canlı doğum (%60) ve 6'sı abortus (%40) ile sonuçlandı. IVF klinik gebelik oranı %20,2, canlı doğum oranı ise %12,1 olarak gerçekleşti. Obstetrik komplikasyonlar arasında preterm doğum, preeklampsi ve fetal büyüme kısıtlılığından oluşan birer vaka yer alıyordu. Anne veya yenidoğan ölümü yaşanmadı ve overyan hiperstimülasyon sendromu vakası bildirilmedi.

Sonuç

Bu çalışmada otoimmün ve otoinflamatuar hastalıkları olan 60 hastada IVF sonuçlarını analiz ettik. IVF prosedürü, nispeten düşük gebelik ve canlı doğum oranları gösterdi. Bununla birlikte, devam eden gebeliklerin yarıdan fazlası canlı doğum ile sonuçlanmıştır. IVF, otoimmün-otoinflamatuar hastalıkları olan hastalarda doğurganlık tedavisi için umut verici bir seçenek olmaya devam etmektedir.

Anahtar Sözcükler

Otoimmün, Otoinflamatuar, İn Vitro Fertilizasyon, İnfertilite, Gebelik

INTRODUCTION

Infertility is defined as the inability to achieve a healthy pregnancy after 12 months or more of regular, unprotected sexual intercourse, or due to an impairment of an individual's or a couple's capacity to conceive (1). The etiology of infertility is believed to be multifactorial, with several key contributing factors, such as genetic abnormalities of both male and female origin, ovulatory disorders, tubal obstructions, and uterine or peritoneal issues associated with female infertility, as well as male factors related to poor sperm quality (2).

The relationship between autoimmune diseases and infertility is influenced by multiple factors. Autoimmune disorders, which are characterized by the presence of autoimmune antibodies and related conditions, can trigger undesirable biological processes such as uterine inflammation, ultimately leading to impaired endometrial receptivity and abnormal placentation (3, 4). The use of cyclophosphamide, which is dependent on severity of the disease, can provoke premature ovarian failure. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) can cause temporary infertility, while corticosteroids have been associated with prolonged time to pregnancy in certain rheumatic diseases (5). Patients with rheumatoid arthritis (RA) often suffer from subfertility which could be a contributing factor to this specific condition (6). In the case of Familial Mediterranean Fever (FMF), infertility is most likely caused by tubo-peritoneal factors and dysovulation (7).

Autoimmune and auto-inflammatory diseases have a dual impact on both infertility and the progression of pregnancy. The consequences of pregnancy with such diseases can exhibit a wide range of outcomes, ranging from improvement of symptoms to worsening, which could potentially result in difficulties for both the mother and the fetus. Although the underlying causes of these differences remain unclear, it is widely believed that complex immunological changes occurring throughout the pregnancy play a crucial role. The changes are defined by the immune tolerance to the paternally inherited antigens expressed by the fetus or trophoblastic cells (8). Obstetric complications commonly associated with higher rates of miscarriage, intrauterine fetal death, fetal growth restriction (FGR), and preterm birth rates (9). Additionally, FMF disease has been associated with increased risk of premature rupture of membranes, recurrent miscarriages, and higher rates of preterm delivery (10).

The thyroid autoimmune disease is associated with the presence of anti-thyroid antibodies which is the most common autoimmune disorder among women who are of childbearing age with a prevalence ranging from 8% to 14% (11, 12). Numerous research studies and meta-analyses have investigated the correlation between thyroid autoimmunity and results of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) (13-15). Howe-

ver, there is limited data available on the outcomes of IVF in patients with non-thyroid autoimmune and auto-inflammatory diseases. In this study, our objective was to assess IVF outcomes in infertile patients diagnosed with at least one auto-inflammatory or autoimmune disease, excluding the most common autoimmune disorder targeting the thyroid gland.

MATERIAL and METHODS

Patients

This retrospective observational study included female patients who had been diagnosed with either an auto-inflammatory disease or non-thyroid autoimmune disease and had at least one IVF procedure at our hospital between January 2014 and January 2023. The present study was assessed by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was granted approval under the designated decision number. The inclusion criteria for the study were as follows: (1) patients diagnosed with either an autoinflammatory disease or a non-thyroid autoimmune disease who had undergone at least one IVF procedure and embryo transfer between January 2014 and January 2023; and (2) women with singleton clinical pregnancies, defined as the presence of an intrauterine gestational sac 4 weeks after embryo transfer. The exclusion criteria were as follows: (1) patients diagnosed with thyroid autoimmune disease who had undergone at least one IVF procedure; and (2) women with biochemical, ectopic and twin pregnancies.

Variables

In this study, the patients' in-patient charts were reviewed from their hospital files. Documentation review included the mean age, mean duration of infertility, etiology of infertility, protocols of ovarian stimulation, complications during and after IVF, ovarian hyperstimulation syndrome (OHSS), and success of IVF (defined by the occurrence of a pregnancy), maternal and fetal complications such as pre-eclampsia, miscarriage, preterm delivery, FGR.

Definitions

Infertility is defined as the inability to achieve conception after one year of regular, unprotected intercourse. IVF procedure refers to the induction of ovulation and oocyte retrieval. This can be followed by embryo transfer in the same cycle or to preserve the embryos for future utilisation as an alternative procedure. The clinical pregnancy rate is calculated as the total number of cycles resulting in clinical pregnancy divided by the total number of transfer cycles. The live birth rate is calculated as the number of cycles resulting in live births divided by the total number of transfer cycles. Additionally, the early abortion rate is defined as the number of cycles experiencing unexpected abortion prior to the 12 weeks of gestation divided by the total number of pregnancy cycles.

Statistical Assessment

The data were analyzed using SPSS software version 20 (IBM, Armonk, NY, United States). The descriptive analyses and quantitative variables are expressed as mean±SD.

RESULTS

Patients

A total of 60 patients were included in the study. The mean age was 33.04 ± 4.5 years, the mean duration of infertility was 4 years (range 2.0–6.2) and the mean body mass index (BMI) was 24.9 ± 5.5. The mean baseline FSH was 8.3 (range 6.3–10) IU/L, the mean E2 level was 44 (range 32–67) pg/mL, and the mean antral follicle count was 4 (range 1–40). Demographic and clinical characteristics of the study patients are shown in Table I.

Table I. Demographics of Patients

Mean age at IVF, yrs	33.04± 4.5
Duration of infertility (IQR), yrs	4 (2.0-6.2)
BMI ± SD, (kg/m2)	24.9 ± 5.5
AFC (number)	5(1-40)
Basal estradiol value (IU/L)	44(32-67)
Basal FSH value (IU/L)	8.3 (6.3-10)
Basal LH value (IU/L)	4.95(0.2-33)

Abbreviations: FSH = Follicle-Stimulating Hormone; LH = Luteinizing Hormone; E2 = Estradiol; AFC = Antral Follicle Count; BMI = Body Mass Index.

RA was the most commonly encountered autoimmune condition, affecting 26.6% of the patients. This was closely followed by FMF, which was present in 25% of the patients. Other autoimmune conditions such as Ankylosing Spondylitis and Behcet's Disease were seen in 6.6% of the patients each, and conditions such as Immune Thrombocytopenic Purpura, Multiple Sclerosis, and Systemic Lupus Erythematosus (SLE) were found in 5% of the patients each. Less common conditions included Crohn's Disease, Urticaria, Psoriasis, each affecting 3.3% of the patients, and Sjögren's Disease, Psoriatic Arthritis, Primary Biliary Cirrhosis with a history of liver transplant, and Type 1 Diabetes Mellitus, each of which were seen in 1.6% of the patients.

The distribution of diseases is shown in Table II.

The treatments administered for these diseases included colchicine in 12/28 cases (42.8%), interferon beta-1a in 1/28 (3.5%), infliximab in 1/28 (3.5%), hydroxychloroquine in 2/28 (7.1%), methylprednisolone in 3/28 (10.7%), salazopyrin in 6/28 (21.4%), triterpene glycosides in 1/28 (3.5%), tacrolimus in 1/28 (3.5%), naproxen sodium in 1/28 (3.5%), anti-TNF alpha in 1/28 (3.5%), and mycophenolic acid in 1/28 (3.5%). Diminished ovarian reserve in 64.9% (39/60), male factor in 20% (12/60), unexplained in 11.6% (7/60), endometriosis in 3.3% (2/60), and tubal factor in 1.6% (1/60) cases were identified as the causes of infertility.

Table II. Distribution of autoimmune and autoinflammatory diseases

Ankylosing spondylitis	4/60(6.6)
Behcet 's Disease	4/60(6.6)
Rheumatoid Arthritis	16/60(26.6)
Familial Mediterranean Fever	15/60(25.0)
Crohn's Disease	2/60(3.3)
Immune Thrombocytopenic Purpura	3/60(5.0)
Multiple Sclerosis	3/60(5.0)
Systemic Lupus Erythematosus	3/60(5.0)
Autoimmune Urticaria	2/60(3.3)
Sjögren's Disease	1/60(1.6)
Psoriasis	2/60(3.3)
Psoriatic Arthritis	1/60(1.6)
Primary Biliary Cirrhosis with Liver Transplant	1/60(1.6)
Type 1 Diabetes Mellitus	1/60(1.6)

Data are expressed as percentages (%).

Table III. Results of IVF and complications during pregnancy

IVF clinical pregnancy rate	15/74 (20.2)
Live birth rate	9/74 (12.1)
IVF-early pregnancy loss rate	6/ 15 (40)
Preterm delivery rate	1/9 (11.1)
Preeclampsia rate	1/9 (11.1)
Cesarean section rate	9/9 (100)
FGR rate	1/9 (11.1)
Mean gestational age, w	37 w 4d
Mean Birth weight, kg	2.99±0.7
Neonatal death	0/9(0)

Data are expressed as percentages (%). Abbreviations: IVF= in vitro fertilization, FGR = fetal growth restriction.

IVF procedure

These women underwent 74 IVF procedures (median per patient: range). Gonadotrophin-releasing hormone antagonist (GnRH) protocol was used in 41 procedures. The progestin-primed ovarian stimulation (PPOS) protocol was used in 20 procedures. Records for 13 treatment procedures could not be accessed. There was no occurrence of OHSS.

IVF and Complications During Pregnancy

In total there were 15 successful pregnancies. Out of 15 pregnancies, there was a total of 9 successful live births (60%) and 6 miscarriages (40%). The clinical pregnancy rate was 20.2%, while the live birth rate was 12.1%. Obstetric complications were preterm birth (n= 1, 6.6%), preeclampsia (n = 1, 6.6%), and FGR (n= 1, 6.6%). A patient who was diagnosed with RA and cervical insufficiency delivered prematurely at 29 weeks of gestation. Preeclampsia was diagnosed in a patient who had a liver transplant due to Primary Biliary Cirrhosis. FGR was observed in a patient diagnosed with SLE. The mean birth weight was measured 2.99±0.7 kg. There were no reports of neonatal death in this sample. Table III displays the results of IVF and any associated complications that occurred during pregnancy.

DISCUSSION

In this retrospective study, records of 60 infertile women who had been diagnosed with either an auto-inflammatory disease or non-thyroid autoimmune disease were admitted to the IVF unit at Akdeniz University. Our findings revealed that the most prevalent cause of infertility in this group was the decreased ovarian reserve, affecting approximately 64.9% of the participants. Ovarian reserve can reflect women's endocrine function and fertility and autoimmune mechanisms contributed to the decrease in the ovarian reserve (16-18). Vega et al. previously demonstrated the correlation between positive immune tests and low levels of anti-Mullerian hormone (AMH) in infertile female patients (19). The study found a significant correlation between the presence of at least one antiphospholipid antibodies (aPL) and reduced AMH levels in a subset of participants. Henes et al. have shown that AMH levels are decreased in individuals with established RA, suggesting that ovarian reserve declines secondary to the RA disease process (20). In addition to autoimmune mechanisms, medications, particularly chronic corticosteroid treatment in patients with RA, have been associated with subfertility and prolonged time to achieve pregnancy. However, this effect was not observed in patients with SLE who were receiving analog treatment (21). In our study, we hypothesise that factors related to autoimmunity, corticosteroid treatment, and possibly postponing pregnancy due to personal reasons may have contributed to the diminished ovarian reserve observed in the study population.

Our study revealed that diminished ovarian reserve is the predominant factor leading to infertility in patients with FMF, impacting 50% of individuals. The association between FMF and infertility has produced contradictory findings in scientific research. Ismajovich et al. discovered that FMF can result in ovarian insufficiency as a result of amyloid accumulation in the ovaries (22). In contrast, Zayed et al. showed that the causes of infertility in FMF patients were similar to those in the general population. Therefore, the observed difference might be attributed to the use of colchicine in FMF patients, which could prevent the complications resulting in infertility (23).

In our series, no cases of OHSS were observed. OHSS is more likely to occur in treatment cycles that utilize human chorionic gonadotrophin (hCG), especially in younger, slender women with polycystic ovarian syndrome, good ovarian reserve, and multiple pregnancies (24). The absence of OHSS in our study could be partly attributed to the use of GnRH antagonist stimulation in some women, the absence of multiple pregnancies, and the 67% reduction in ovarian reserve within the study cohort.

In our current study, the IVF clinical pregnancy rate was 20.2%, while the live birth rate was 12.1%. These rates were lower than those reported for 'low risk' IVF pregnancies and similar to the poor ovarian responder group (25-28). The lower implantation success and live birth rates observed in our study may be attributed to the decreased ovarian reserve identified in nearly 65% of the patient population. Prematurity rates in IVF pregnancies have been reported to vary significantly, ranging from 10% to 54%, while pre-eclampsia rates are estimated to be in the range of 3% to 6% for such pregnancies (29, 30). In our study, pregnancy complications were found to be similar to those seen in low-risk IVF pregnancies. However, direct comparison of our results with these values is challenging due to variability in reporting, study heterogeneity, and the limited number of patients in our study.

This study demonstrated a miscarriage rate of up to 40%. It is widely recognized that the spontaneous miscarriage rate following IVF, which can reach approximately 15%, is higher than that observed after natural conception. One potential explanation is that women undergoing IVF treatment are typically of advanced maternal age. Both ovarian reserve and oocyte quality decline significantly with increasing age, contributing to the elevated risk of miscarriage in this population. In addition, advanced maternal age has been associated with an increased incidence of oocyte chromosomal abnormalities across all human populations (31). Moreover, the causes of diminished ovarian reserve include autoimmune diseases, inherited chromosomal and genetic disorders, environmental hazards, and iatrogenic factors; however, a substantial proportion remains unexplained (32).

Women with diminished ovarian reserve are prone to reproductive decline, experiencing exceptionally high rates of pregnancy loss during ART treatments (8, 33). The reasons for the high miscarriage rate in our study might be that our patient population includes women of relatively advanced age and decreased ovarian reserve due to autoimmunity.

We observed preterm delivery in one patient with RA and cervical insufficiency. Women with RA have an increased risk of preterm delivery, attributed to the severity of the disease and the use of glucocorticoid (34). We speculated that cervical length measurement and follow-up may contribute to the prevention of preterm labor in pregnant women complicated with RA, especially in those using steroids.

In our study, preeclampsia developed in a patient who had a liver transplant following Primary Biliary Cirrhosis. The consequences of chronic liver disease and liver transplantation may delay both timing and ability of women to conceive. The majority of patients have an improvement in sub-fertility after undergoing a liver transplant (70–95%). Although subfertility often improves following liver transplantation, it is possible for subfertility to continue due to liver-related factors, such as the use of immunosuppressant drugs or complications that arise after the transplantation (35). Rahim et al. provided a detailed account of a series of cases that outlined the results of IVF in women who have liver disease and have undergone a liver transplantation. The rates of clinical pregnancy and live birth per cycle were found to be consistent with the general population. The pregnancy was complicated by hypertensive disorders, intrahepatic cholestasis of pregnancy, and preterm delivery (36).

The main limitations of our study include its comparatively limited and heterogeneous sample size, retrospective methodology, and its depiction of the experience of a single center. As a result, we were unable to retrieve data regarding the levels of autoantibodies associated with autoimmune disorders from the patients' medical records.

CONCLUSION

In conclusion, this study provides insight into IVF outcomes in patients with auto-inflammatory and rare autoimmune diseases. Overall, IVF seems to have comparatively low rates of pregnancy and live birth, which are similar to the rates observed in individuals with poor ovarian response. Over 50% of the pregnancies that occurred as a result of IVF led to successful live deliveries, without neonatal deaths. IVF remains a promising option for fertility treatment in patients with autoimmune diseases. Customizing IVF treatments for these specific patient groups, considering variables such as high daily doses of prednisone or NSAID therapies, suppression of disease activity, and utilising multidisciplinary approaches, has the potential to enhance pregnancy outcomes. Further research is needed for the validation of our findings to offer more reliable recommendations for patients with autoinflammatory and autoimmune diseases.

Ethical Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Akdeniz Medical Faculty Ethical Committee, Akdeniz University (approval number: 2023/ KAEK-291).

Informed Consent

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions

Concept - G.A.B., S.M.C.; Design - Ü.Z., O.F., C.B.; Supervision - C.Y.S.; Resources - G.A.B., S.M.C. E.K., Materials - S.M.C.; Data Collection and/or Processing - G.A.B., S.M.C.; Analysis and/or Interpretation - G.A.B., E.K.; Literature Search - Ü.Z., A.A., F.Ç.; Writing Manuscript - G.A.B.; Critical Review – Ş.O., M.Ö., C.Y.S., İ.M.

Conflict of Interes

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

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