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Systematic Review (Pages: 29-40)

The Effects of Immunosuppressive Treatments on Pregnancy Outcomes in Infertile Women: A Systematic Review of Clinical Trials

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Abstract

Background: Despite advancements in in-vitro fertilization (IVF), repeated implantation failure (RIF) remains a significant obstacle to fertility. Immunomodulation and immunosuppression are key strategies to address RIF. This study reviews the literature on the effects of immunosuppressive drugs on pregnancy outcomes in infertile women with RIF.

Materials and Methods: For this systematic review, two independent reviewers selected relevant articles from Scopus, EMBASE, the Cochrane Central Register of Controlled Trials, the International Registry Platform for ongoing trials, ClinicalTrials.gov, Web of Science, CINAHL, Medline, and Google Scholar. The search covered all available literature up to January 2023, without time restrictions.

Results: Combining prednisone and hydroxychloroquine (HCQ) significantly improves fertilization, implantation, and clinical pregnancy rates compared to prednisone alone, offering a promising immunomodulatory approach for women facing fertility challenges. HCQ modulates immune responses by reducing Th17-related cytokines and increasing T-reg-related cytokines, while also decreasing TNF-α and increasing IL-10 levels. Although abortion rates remain similar, adding cyclosporine to the regimen does not significantly improve outcomes. These findings suggest that prednisone with HCQ may be more effective than prednisone alone for specific patient populations.

Conclusion: Combining prednisone and HCQ significantly improves fertility outcomes by enhancing immune modulation. This combination offers a promising approach for women facing specific fertility challenges, although adding cyclosporine does not yield additional benefits in certain outcomes. Overall, HCQ's immunomodulatory effects support its potential in enhancing reproductive health.

Key Words: Immunosuppressive treatment, Infertility, Pregnancy, Outcomes, Reproductive

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1- INTRODUCTION

Infertility is a condition that affects the male or female reproductive system and is defined as the inability to conceive after 12 months or more of regular unprotected sexual intercourse (1). It impacts millions of people of reproductive age worldwide, affecting not only individuals but also their families and communities. Estimates suggest that approximately 48 million couples and 186 million individuals live with infertility globally (2-4).

Assisted reproductive technology (ART) encompasses all fertility treatments in which eggs or embryos are handled outside the body. Generally, ART procedures involve retrieving mature eggs from a woman's ovaries using a needle, combining the eggs with sperm in a laboratory setting, and returning the embryos to the woman's body or donating them to another woman. The primary type of ART is in vitro fertilization (IVF) (5).

Assisted reproductive technology has made considerable advancements since its inception; however, the current success rate remains below 30%, and implantation failure continues to be a significant challenge in female fertility (6). Approximately 25-40% of natural implantations are lost, and loss of implantation occurs in 75% of pregnancies that are not clinically recognized. Recently, immunological factors have garnered attention from scientists as potential causes of reproductive failure (7).

Recurrent implantation failure refers to the inability to achieve a clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in women under 40 years of age (8). Repeated implantation failure (RIF), also known as IVF failure, occurs when transferred embryos fail to implant, resulting in no pregnancy. RIF is specifically defined as the absence of pregnancy after at least three fresh or frozen embryo transfers (FET) to the uterus (8). Immunosuppressants have been widely used since the late 20th century for various indications (9). Currently, immunosuppressive drugs are employed in the treatment of inflammatory and autoimmune diseases, as well as in transplantation (10). Additionally, the suppression and regulation of the immune system through immunomodulatory or immunosuppressive agents are key strategies for reducing recurrent implantation failure (11, 12).

Hydroxychloroquine, an antimalarial drug, is commonly used in patients with various autoimmune diseases, particularly systemic lupus erythematosus (SLE). This drug possesses anti-inflammatory and immune-regulatory properties, including inhibiting phospholipase A2 activity, stabilizing lysosomal membranes, blocking the production of several pro-inflammatory cytokines (e.g., TNF-α, IL-17, IL-6, IFN-α, and IFN-γ), decreasing complement-dependent antigen-antibody reactions, and modulating T-cell subsets such as enhancing regulatory T cells or suppressing effector T cells (13).

Immunosuppressants are often the first choice for treating inflammatory and autoimmune disorders and are prescribed for both young and elderly patients. However, the continued use of these medications in women may have adverse effects on fertility, pregnancy outcomes, and the unborn child (9). Despite significant recent advances in in vitro fertilization (IVF), RIF remains a serious challenge to fertility (10). Immune cell disorders, such as cytokine imbalances and alterations in the Th1/Th2 ratio, have been reported as potential causes of RIF (14). The present study aims to review the literature on the effects of immunosuppressive drugs on pregnancy outcomes in infertile women with RIF.

2- MATERIALS AND METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (15).

2-1. Eligibility criteria

The Participants, Interventions, Comparators, and Outcomes (PICO) framework guided the development of the review objectives and inclusion criteria.

2-1-1. Participants: Women experiencing infertility due to recurrent implantation failure (RIF).

2-1-2. Interventions: Exposure to any immunosuppressive drug (e.g., hydroxychloroquine, cyclosporine, intravenous immunoglobulin [IVIG], or prednisone) within six months before or during conception.

2-1-3. Comparators:

- Treatment group versus control group.
- Treatment group versus different treatment types.
- Pre-treatment versus post-treatment.

2-1-4. Outcomes:

- **Primary Outcomes**: Changes in biochemical pregnancy rate, fertilization rate, live birth rate, clinical pregnancy rate, implantation rate, and abortion rate.
- **Secondary Outcome**: Significant changes in Th1/Th2 balance and Th17/Treg ratio.

2-2. Included Studies

Included studies comprised randomized controlled trials (RCTs), randomized and non-randomized clinical studies, as well as retrospective and prospective studies that assessed the effect of hydroxychloroquine on infertile women with recurrent implantation failure (RIF). Studies were eligible for inclusion if they were published in English or Persian and contained original data on the exposure of infertile women to immunosuppressive drugs, published up to January 2023.

2-3. Exclusion criteria

The exclusion criteria included abstracts without full articles, articles not written in English or Persian, review articles, pilot studies, letters, editorials, short reports, case reports, and preliminary or brief studies.

2-4. Information sources

A systematic search of electronic databases was conducted, including Medline (via PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), the International Registry Platform for ongoing trials, ClinicalTrials.gov, EMBASE, Web of Science, Scopus, and the Google Scholar search engine.

2-5. Search

The search terms consisted of a combination of keywords related to fertility and pregnancy outcomes, along with a list of immunosuppressive drugs: (Hydroxychloroquine OR Immunosuppressive agents) AND (RIF OR Infertility OR Pregnancy OR Abortion OR Pregnancy outcomes OR Fertilization rate OR Live birth rate OR Clinical pregnancy OR Implantation rate OR Biochemical). The search was conducted independently and in duplicate by two reviewers, and any disagreements between the reviews were resolved by the supervisor. Additionally, references from the primary search publications were included if relevant data were missed during the search.

2-6. Study selection

A database search was conducted to identify potential studies. Abstracts were screened for eligibility, full-text articles were obtained and assessed, and a final list of included studies was compiled. In

addition to primary articles, their references were also searched for additional studies. This process was carried out independently and in duplicate by two reviewers, with any disagreements resolved by a third reviewer. References were organized and managed using EndNote software (version X8).

2-7. Data collection process

A researcher-developed template was created and used for each study. Two reviewers independently collected the data, and any discrepancies were resolved by a third reviewer. The data gathered from the selected studies included the study design, study population (which encompassed authors' names, year of publication, sample size, and age group), types of interventions and comparisons applied, as well as the main results.

2-8. Risk of bias in individual studies

The final version of the Jadad scale was used to assess the quality of the trials. This scale comprises three key components, each scored from 0 to 5 points. These components include:

- Randomization: Whether randomization was conducted and if it was done appropriately.
- Blinding: Whether the trial was blinded and if it was implemented correctly.
- Reporting of Withdrawals and Dropouts: Whether the rates and reasons for withdrawals and dropouts were adequately reported (16).

The quality of retrospective studies was evaluated using the Newcastle-Ottawa Scale (NOS) (17) (**Table 1**). Two reviewers independently conducted the assessments in duplicate, with any discrepancies resolved by a third reviewer.

2-9. Synthesis of results

A meta-analysis was unfeasible due to significant heterogeneity in study designs, interventions (e.g., IVIG, HCQ, Prednisone), and outcomes (e.g., live birth rates, cytokine levels), making it difficult to draw generalized conclusions.

2-10. Ethical considerations

Approval from a research ethics committee was not necessary, as the study analyzed only publicly available articles. The research adhered to ethical standards by respecting copyright laws and ensuring transparency in its methods and sources.

3- RESULTS

A total of six relevant studies (n = 447 subjects) met the inclusion criteria for this systematic review (**Figure 1**). The main characteristics of the selected studies are summarized in **Table 1** and described below:

3-1. The Effect of Immunosuppressive Treatment on Pregnancy Outcomes

Ahmadi et al. investigated the impact of intravenous immunoglobulin G (IVIG) on the function and frequency of T-regulatory (T-reg) and Th17 cells, which are key CD4+ T cell subclasses related to pregnancy and implantation rates. The study included 72 patients with RIF who had elevated preconception Th1/Th2 ratios and increased natural killer (NK) cell activity. Participants were divided into two groups: one receiving IVIG, aspirin, and enoxaparin (n = 40, treatment group), and the other receiving only aspirin and enoxaparin (n = 32, control group).

The analysis of Th17 and T-reg frequencies, transcription factors, cytokine gene expression, and cytokine secretion was conducted using flow cytometry, real-time PCR, and ELISA techniques. In the IVIG treatment group, post-treatment evaluations indicated a significant increase in T-reg-related parameters: T-reg frequency ($p = 0.018$), Foxp3 levels ($p<0.001$), and cytokine mRNA levels for IL-10 ($p = 0.0058$) and TGF-β ($p= 0.0038$)

(7). Conversely, a significant difference was observed in Th17 cells, where only a decrease in the mRNA level of RORγt was noted (p = 0.021) (7).

In a retrospective study conducted by Meng et al. (18), women experiencing IVF-ET failure were examined from January 2019 to March 2020. The results revealed an increase in the Th1/Th2 ratio, with an elevated ratio of ≥10.3. Patients were categorized into treatment and control groups based on whether they received immunoregulatory treatment (PDN + HCQ + CsA / PDN + HCQ / PDN = 21 / 9 / 11) during the frozen transfer cycle, comprising a treatment group of 41 patients and a control group of 30 patients. While baseline profiles were similar between the two groups, the treatment group showed a significantly higher live birth rate (41.5% vs. 16.7%, p = 0.026). The treatment group also exhibited higher, though not statistically significant, rates of biochemical pregnancy (56.1% vs. 40%, p= 0.18), implantation (36.5% vs. 23.9%, p = 0.15), and clinical pregnancy (51.2% vs. 30%, p = 0.0743) compared to the control group (18).

In a retrospective study, Lian et al. (19) examined 156 patients who underwent IVF-ET with positive ANA and ds-DNA but without symptoms in South China from January 2010 to December 2016. Patients received either prednisone (7.5 mg/day) or a combination of prednisone (7.5 mg/day) and hydroxychloroquine (HCQ) (0.2 g twice daily) before and during pregnancy, with IVF-ET outcomes and complications assessed. The two groups—prednisone (n = 65) and prednisone + HCQ (n = 91)—showed no significant differences in demographic characteristics or reproductive indices, including duration of infertility, basal sex hormone levels, total Gn dose, E2 level on the day of HCG initiation, and the number of retrieved oocytes.

The prednisone + HCQ group exhibited significantly higher rates of fertilization (75.8% vs. 60.0%, p = 0.017), implantation (29.7% vs. 15.4%, p = 0.032), and clinical pregnancy (62.6% vs. 47.7%, p = 0.028) compared to the prednisone group, along with insignificantly lower abortion rates (7.0% vs. 12.9%). There was no correlation between clinical pregnancy rates and ANA or ds-DNA levels, while implantation failure was associated with low C3 levels. Neither group experienced complications that affected the treatment period (19).

Sadeghpour et al. conducted a clinical trial to investigate the effects of HCQ on Th17 and T-regulatory (T-reg) cell levels and functions in women with recurrent implantation failure (RIF). They found no significant difference in biochemical pregnancy rates among RIF patients before and after HCQ treatment (20).

3-2. The Effect of Hydroxychloroquine Treatment on Modulating the Th1/Th2 Balance and Th17/T-reg Ratio in Women with Recurrent Implantation Failure (RIF)

Ghasemnejad-Berenji et al. examined patients (n = 17) experiencing Recurrent Implantation Failure (RIF) for elevated Tumor Necrosis Factor-alpha (TNF-α)/Interleukin-10 (IL-10) ratios (TNF-α/IL-10 ≥ 30.6) before and after oral administration of Hydroxychloroquine (HCQ) at a dose of 400 mg/day. HCQ resulted in a significant reduction in serum TNF-α levels (p < 0.0001) and an increase in serum IL-10 levels (p < 0.0001). The expression of T-bet, a Th1 transcription factor, was downregulated, while that of GATA-3, a Th2 transcription factor, was upregulated. There was a significant increase in the fluorescent immunoreactivity of Interleukin-4 (IL-4) and IL-10 (p < 0.05), as well as a significant decrease in the fluorescent immunoreactivity of TNF-alpha and Interferon-gamma (IFN-γ) in endometrial

tissue following HCQ treatment (21). This study indicates that HCQ may effectively modulate the Th1/Th2 balance and improve immune responses in women with RIF, potentially contributing to better pregnancy outcomes.

Table-1: General characteristics of the included studies (n=6).

Author/Year/ Country, (Reference)	Study designs	Age (years), mean± SD	Sample size	Intervention (dose and duration)	Comparison (dose and duration)	Main results	Quality assessment
Ahmadi et al., 2017, Iran, (7)	Clinical trial	Intervention group:36.8 ±2.7, Control group: 37.1± 2.4	72	Patients received IVIG, aspirin, and heparin (enoxaparin); n=40.	Patients received aspirin and heparin (enoxaparin); n = 32.	In the IVIG group, there was a significant difference in T-regulatory (Treg) indices, including Treg frequency (p = 0.0186), Foxp3 levels (p = 0.0004), and cytokine mRNA levels (IL-10: p = 0.0058; TGF-β: p = 0.0038). However, a significant difference was observed for Th17 only, with a decrease in the mRNA level of RORγt (p = 0.0218).	4*
Meng et al., China, 2020, (22)	Retrospective cohort	Intervention group: 34.61±4.05, Control group: 34.57±3.42	71	Received PDN + HCQ + CsA, PDN + HCQ, or PDN; n = 41.	No immunoregulatory treatment; n= 30.	The rate of live birth was higher in the treated group compared to untreated patients (41.5% vs. 16.7%, p = 0.026). The rates of biochemical pregnancy (56.1% vs. 40%, p = 0.18), implantation (36.5% vs. 23.9%, p = 0.15), and clinical pregnancy (51.2% vs. 30%, p = 0.0743) were also higher in the treated group than in the control group; however, these differences were not statistically significant except for live birth rates, which showed a significant difference between groups.	**15
Lian et al., 2018, China, (19)	Retrospective cohort	-	156	Received prednisone (7.5 mg/day); n = 65, or prednisone (7.5 mg/day) + HCQ (0.2 mg twice daily); n = 91.		The fertilization rate, implantation rate, and clinical pregnancy rate were significantly higher in the prednisone + HCQ group compared to the prednisone-only group (75.8% vs. 60.0%, p = 0.017; 29.7% vs. 15.4%, p = 0.032; and 62.6% vs. 47·7%, p = ·028, respectively). Although the abortion rate was lower in the prednisone + HCQ group (7·0% vs ·12·9%), this difference did not reach statistical significance. These findings suggest that combining prednisone with hydroxychloroquine may be more effective than using prednisone alone for patients undergoing IVF-ET, particularly those with positive ANA and ds-DNA.	**14

Sadeghpour et al., 2020, Iran, (20)	Clinical trial (before and after intervention)	33.6± 4.2	60	Received HCQ at 400 mg per day for 16 days; n = 60.	-	Treatment with HCQ significantly decreased Th17-related cytokines and their function while significantly increasing T-reg-related cytokines and their function ($p < 0.001$). Additionally, the expression levels of RORγt and FOXP3 were also altered, with an increase in FOXP3 but potentially a decrease in RORγt given its association with Th17 cells. However, despite these immunological changes, the biochemical pregnancy rate did not show a significant difference in patients with RIF before and after treatment.	*3
Ghasemnejad-Berenji et al., 2018, Iran, (21)	Clinical trial (before and after intervention)	33.6 ± 4.2	17	Received HCQ at 400 mg orally per day.	-	Hydroxychloroquine administration in women with RIF and a high TNF-α/IL-10 ratio during the implantation window can reduce this ratio.	*4
Meng et al., China, 2022, (18)	Retrospective cohort study	Intervention group: 34:61± 4:05, Control group: 4:57± 3:42	71	Received PDN, HCQ, and CsA.	-	Immunoregulatory therapy appears to improve reproductive outcomes in women with an elevated Th1/Th2 cytokine ratio who experience embryo transfer failure.	**15

* Jadad scale, ** Newcastle-Ottawa Scale. SD: Standard deviation, IVIG: Intravenous immunoglobulin, IL-10*:* Interleukin 10, TGF- β: Transforming growth factor beta, Th17: T helper type 17, *mRNA*: messenger ribonucleic acid, PDN: Prednisone, HCQ: Hydroxychloroquine, CsA: Cyclosporine, RORγt: Retineic-acid-receptor-related orphan nuclear receptor gamma, RIF: Repeated implantation failure, Th1: T helper type 1, Th2: T helper type 2, TNF-α*:* Tumour necrosis factor alpha, ANA: Antinuclear antibodies, ds-DNA: Double-stranded DNA.

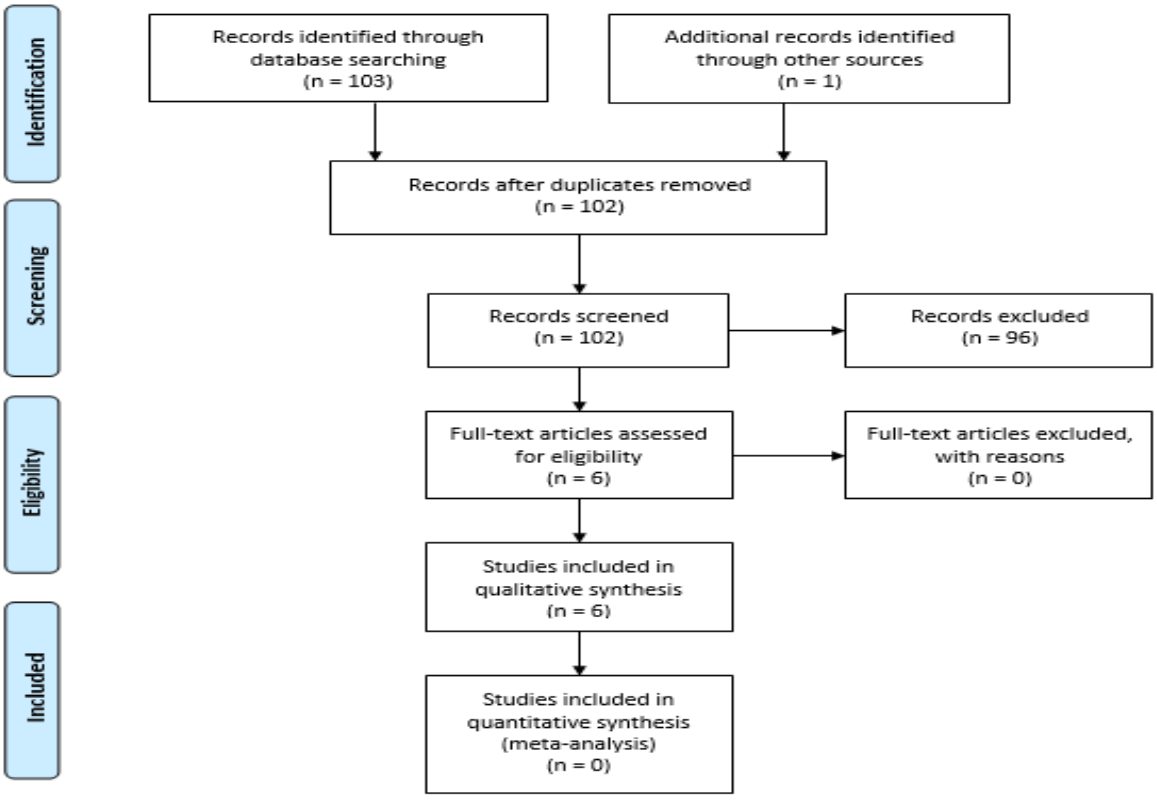

Fig.1: PRISMA Flowchart.

4- DISCUSSION

This systematic review aimed to explore the literature on the effects of immunosuppressive drugs on pregnancy outcomes, including fertilization, live birth, clinical pregnancy, implantation rates, abortion rates, and biochemical pregnancy in infertile women who have experienced Recurrent Implantation Failure (RIF). Based on the gathered results, immunoregulatory agents may be effective in improving fertilization and live birth rates as well as clinical pregnancy and implantation rates; however, they do not appear to reduce abortion or biochemical pregnancy rates.

Infertility is defined as a condition of the human reproductive system where the body fails to achieve pregnancy after regular unprotected sexual intercourse. The World Health Organization (WHO) characterizes infertility as a chronic health disorder affecting men and women worldwide (22). In their study, Meng et al. demonstrated that HCQ treatment in patients with RIF and impaired immune cells during pregnancy influenced the Th17/T-reg ratio by increasing T-reg cells and reducing Th17 responses. This contributed to successful pregnancy outcomes. However, current research found no significant difference in these outcomes due to limitations such as a small sample size (18).

Based on the findings, the abortion rate was lower in the prednisone + HCQ group compared to the prednisone group (7.0% vs. 12.9%), although this difference was not statistically significant (19). The live birth rate is defined as the delivery of at least one live-born infant after 24 weeks of gestation (23). According to the results, groups treated with prednisone + HCQ + Cyclosporin A (CsA), prednisone + HCQ, and prednisone alone had higher live birth rates compared to untreated patients; specifically, a significant difference was observed between these treatment groups and untreated patients (41.5% vs. 16.7%, p= 0.026) (22).

Clinical pregnancy is defined as the presence of positive serum human Chorionic Gonadotropin (hCG) and a confirmed gestational sac on ultrasound or clinical findings of trophoblasts (24). Based on the results, clinical pregnancy rates were higher in groups treated with immunoregulatory agents compared to the control group (51.2% vs. 30%, p = 0.0743), although this difference was not statistically significant (22). Additionally, clinical pregnancy rates were significantly higher in the prednisone + Hydroxychloroquine (HCQ) group than in the prednisone-only group (62.6% vs. 47.7%, p = 0.028) (19). Furthermore, treatment with immunoregulatory agents improved clinical pregnancy rates in patients experiencing Recurrent Implantation Failure (19).

Implantation is defined as the process by which the embryo attaches to the endometrial surface of the uterus, invades the epithelium, and subsequently establishes maternal circulation to form the placenta (25). According to the results, implantation rates were higher in groups receiving immunoregulatory treatment compared to those in the control group (36.5% vs. 23.9%, p = 0.15), although this difference was not statistically significant (22). Conversely, implantation rates were significantly higher in groups treated with prednisone + HCQ compared to those treated with prednisone alone (29.7% vs. 15.4%, p = 0.032) (19). Moreover, combining HCQ as an immunosuppressive agent with prednisone improved implantation rates compared to using prednisone only (18).

The fertilization rate is defined as the total number of embryos divided by the total number of retrieved oocytes (26). Based on the results, fertilization rates were significantly higher in groups treated with prednisone + HCQ compared to those

treated with prednisone alone (75.8% vs. 60.0%, p = 0.017) (19).

Biochemical pregnancy is defined by the detection of hCG levels in blood or urine, often accompanied by clinical symptoms of pregnancy. Clinical pregnancy, on the other hand, refers to the observation of an intrauterine gestational sac via ultrasound (27-29). In a study by Meng et al., the immunoregulatory treatment group demonstrated a higher biochemical pregnancy rate compared to the control group (56.1% vs. 40%, p = 0.18), although this difference was not statistically significant (16). Sadeghpour et al. found no significant difference in biochemical pregnancy rates among patients with RIF before and after treatment with HCQ (20). While immunoregulatory treatments showed a higher biochemical pregnancy rate, this finding was not statistically significant. These results should be interpreted cautiously due to limitations such as a small sample size (18).

The use of antimalarial agents in infertile individuals is a topic of debate, as long-term use or high doses can potentially induce ocular toxicity and even irreversible retinopathy in some cases. It has been reported that HCQ levels in cord blood are nearly as high as those in maternal blood. Animal studies have indicated ocular drug accumulation in fetal mice (30). A systematic review found that out of 1,477 infants exposed to HCQ or chloroquine, 789 were documented; overall, 563 exposed infants were followed postnatally (ranging from less than three months to 19 years), with 331 undergoing ophthalmologic examinations during follow-up (31). The literature review revealed a low-to-nonexistent risk of visual abnormalities in offspring exposed to antimalarial drugs (31). Additionally, another systematic review found that patients with autoimmune disorders showed no indication of an elevated risk of congenital defects, spontaneous abortions, fetal death, prematurity, or reduced live birth rates when using these medications (32).

4-1. Study Limitations

The differences between the studies included in this systematic review may be attributed to varying definitions of Recurrent Implantation Failure (RIF) across the studies. Additionally, the prevalence of RIF varies significantly across different communities, ranging from 10% to 30% (11). The duration of infertility is a significant criterion for predicting pregnancy outcomes; couples who have been infertile for less than three years generally have a higher odds ratio for achieving pregnancy. Therefore, confounding factors should be carefully examined in future studies. There is a need for prospective randomized trials to investigate the efficacy and safety of immunotherapy during frozen embryo transfer cycles. Furthermore, these results may not be generalizable to patients undergoing fresh embryo transfers.

5- CONCLUSION

Immunosuppressive treatments, particularly combinations involving hydroxychloroquine (HCQ) and prednisone, have shown potential in enhancing pregnancy outcomes for women experiencing Recurrent Implantation Failure (RIF). These therapies modulate immune responses by adjusting the Th1/Th2 balance and regulating T-reg and Th17 cells, which can significantly improve fertilization rates, clinical pregnancy rates, live birth rates, and implantation success. Additionally, HCQ treatment has been found to influence the Th17/T-reg ratio in patients with RIF and impaired immune cells during pregnancy.

Overall, while safety considerations must be carefully managed due to potential risks associated with long-term use of certain immunosuppressants like HCQ, the

available evidence suggests that these treatments can be relatively safe when used judiciously under medical supervision. Immunoregulators may be beneficial for improving fertility outcomes by addressing immunological disturbances; however, they do not appear to reduce abortion or biochemical pregnancy rates significantly. Future research should focus on confirming these findings through larger-scale prospective randomized trials to solidify their efficacy and safety profiles. These studies should also consider generalizability across different embryo transfer types (fresh vs frozen) due to current limitations in study designs.

6- ABBREVIATIONS

ART: Assisted Reproductive Technology
IVF: In Vitro Fertilization
RIF: Recurrent Implantation Failure
FET: Frozen Embryo Transfer
SLE: Systemic Lupus Erythematosus
TNF-α: Tumor Necrosis Factor Alpha
IL-17: Interleukin 17
IL-10: Interleukin 10
IL-6: Interleukin 6
IL-4: Interleukin 4
IFN-α: Interferon Alpha
IFN-γ: Interferon Gamma
T-reg: Regulatory T Cells
IVIG: Intravenous Immunoglobulin
Th1: T Helper Type 1
Th2: T Helper Type 2
Th17: T Helper Type 17
CD4+ T Cells: T Helper Cells
Real-time PCR: Real-time Polymerase Chain Reaction
ELISA: Enzyme-Linked Immunosorbent Assay
Foxp3: Forkhead Box P3
mRNA: Messenger Ribonucleic Acid
TGF-β: Transforming Growth Factor Beta
RORγt: Retinoic Acid Receptor-Related Orphan Nuclear Receptor Gamma
IVF-ET: In Vitro Fertilization - Embryo Transfer Failure
PDN: Prednisone
HCQ: Hydroxychloroquine
CsA: Cyclosporine
ANA: Antinuclear Antibodies
ds-DNA: Double-Stranded DNA
GATA3: GATA Binding Protein 3
C3: Complement 3
E2: Estradiol.

7- CONFLICT OF INTEREST: None.

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