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Research Article | Araştırma Makalesi

EFFECT OF INTRAVENOUS LIPID (SMOFLIPID®) USE ALONG IN VITRO FERTILIZATION (IVF) TREATMENT IN WOMEN WITH FAILED IVF CYCLES DESPITE GOOD QUALITY EMBRYO TRANSFER: CASE-CONTROL STUDY

KALİTELİ EMBRİYO TRANSFERİNE RAĞMEN BAŞARISIZ IVF SİKLUSU OLAN KADINLARDA İN VİTRO FERTİLİZASYON (IVF) TEDAVİSİ BOYUNCA İV LİPİD (SMOFLIPID®) KULLANIMININ ETKİSİ: VAKA KONTROL ÇALIŞMASI

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ABSTRACT

Objective: Since recurrent implantation failure (RIF) is a challenging fact, effects of different therapeutic immunomodulatory agents are being investigated to overcome this problem. This study aimed to evaluate the effect of intralipid on pregnancy outcomes of IVF patients with RIF.

Methods: 116 of the participants who received only the short antagonist protocol allocated in the control group, whereas 106 patients were in intralipid group by additionally receiving intravenous lipid (SMOFlipid®). Intralipid was given on the day of embryo transfer, on the day of positive pregnancy test and continued weekly until the tenth week of pregnancy. Implantation rate, biochemical pregnancy rate, clinical pregnancy rate and live birth rate were evaluated.

Results: The positive pregnancy test, clinical pregnancy rate and live birth rate were statistically significantly higher ($p<0.001$) in the intralipid group (50.9% vs. 22.4%, 41.5% vs. 19.8%, 29.2% vs. 10.3%, respectively). There was not significantly difference between groups in terms of implantation, spontaneous abortion, multiple pregnancy, and chemical pregnancy rates ($p>0.05$).

Conclusion: This study revealed that intralipid therapy has better pregnancy outcomes in patients with RIF compared to patients undergo standard IVF protocol only. Further prospective studies are needed to suggest the routine use of intralipid in patients with RIF.

Keywords: *In Vitro* fertilization, intravenous lipid emulsions, embryo implantations

ÖZ

Amaç: Tekrarlayan implantasyon başarısızlığı (RIF) zorlu bir gerçek olduğundan, bu sorunun üstesinden gelmek için farklı terapötik immünomodülatör ajanların etkileri araştırılmaktadır. Bu çalışma, intralipidin RIF'li IVF hastalarının gebelik sonuçları üzerindeki etkisini değerlendirmeyi amaçlamıştır.

Yöntem: Katılımcıların 116'sı sadece kısa antagonist protokolünü alan kontrol grubuna, 106'sı ise intravenöz lipid (SMOFlipid®) verilerek intralipid grubunda yer aldı. İntralipid, embriyo transferinin olduğu gün, pozitif gebelik testinin olduğu gün verildi ve gebeliğin onuncu haftasına kadar haftalık olarak devam edildi. İmplantasyon oranı, biyokimyasal gebelik oranı, klinik gebelik oranı ve canlı doğum oranı değerlendirildi.

Bulgular: Pozitif gebelik testi, klinik gebelik oranı ve canlı doğum oranı İntralipid grubunda istatistiksel olarak anlamlıydı ($p<0,001$) (sırasıyla %50,9'a karşı %22,4, %41.5'e karşı %19,8, %29,2'ye karşı %10,3)). İmplantasyon, spontan abortus, çoğul gebelik ve kimyasal gebelik oranları açısından gruplar arasında anlamlı fark yoktu ($p>0.05$).

Sonuç: Bu çalışma, intralipid tedavisinin, sadece standart IVF protokolü uygulanan hastalara kıyasla RIF'li hastalarda daha iyi gebelik sonuçlarına sahip olduğunu ortaya koymuştur. RIF'li hastalarda intralipidin rutin kullanımını önermek için daha ileri prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: I*n vitro* fertilizasyon, intravenöz lipid emülsiyonları, embriyo implantasyonları

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Introduction

Recurrent implantation failure (RIF) is defined as failure of implantation despite good quality embryo transfer in more than one in vitro fertilisation (IVF) cycle.[1] RIF is a discouraging fact for couples and physicians.[2] The maximum implantation success achieved in many assistive reproductive technology (ART) centers varies between 40-60%.[3] One-tenth of couples receiving IVF or intrastoplasmic sperm injection (ICSI) experience repeated implantation failure.[4] The mechanism of embryo implantation, where endometrial receptivity plays an important role, is a complicated process and its treatment is still unclear. There are many reasons that can lead to implantation failure. Apart from embryo related factors maternal factors such as uterine anomalies, thrombophilia, immunological problems can be counted among these reasons. Although uterine problems and thrombophilias are routinely tested in patients with IVF, immunological factors are not effectively screening.[5]

Immune dysfunction in the endometrial environment has been raised as an etiology in recent years and the role of immunomodulators in the treatment of this group of patients has started to be focused on.[2] Some different therapeutic immunomodulating agents such as intravenous immunoglobulin, progesterone, low molecular heparin, prednisone, local or systemic granulocyte colony-stimulating factor and intralipid are used due to their potential benefits in IVF/ICSI cycles.[6-7] However we still lack the evidence of their efficacy on implantation.

Intravenous lipid therapy is a sterile, nonpyrogenic parenteral nutrition that includes soybean oil as active component, egg phospholipids and glycerin. Although the immune mechanism of intralipid is still not well known;[8] it is hypothesized to inhibit pro-inflammatory mediators, decrease IL-2 production, TNF-a, IL-1β, and suppress natural killer cell levels activity.[8-9] A large evidence revealed that intravenous lipid has positive effect on the treatment of some medical problems such as verapamil toxicity, malathion-induced hepatotoxicity and chronic intestinal failure.[10-11]

In the literature, there are few solid data about using intravenous lipid as a feasible, safe, cost-effective agent in the treatment of RIF patients.[12-13]

In this study, it was aimed to investigate the effect of intravenous lipid on outcomes measured in terms of implantation rate and pregnancy rate in patients with unexplained RIF undergoing IVF/ICSI.

Methods

In this study, records of 6052 patients applied to Konsultan IVF Centres between January 2017-January 2018 were retrospectively evaluated. Patients who had IVF failure despite at least two high quality embryo transfer previously, aged under 45, with normal hormone profile (FSH, LH, TSH, PRL, AMH) were included in the study. Prior to the enrollment the hysterescopy and hysterosalphingography reports of patients and semen analysis of the partners were evaluated. A total of 5810 patients who may had implantation failure due to some contrubuting factors such as paternal genetic abnormality, infertility caused by male factor like severe azoospermia, low-quality embryo or fertilization failure; with poor ovarian reserve, have endometriosis or anatomical abnormalities such as hydrosalpinx, uterine adhesion, polyp, or fibroids and those with positive thrombophilia were excluded from the study. Women that have medical contraindications of intralipid infusion with known allergic predisposition to eggs, lecithin, or soy products were excluded as well. Out of 242 patients, 20 patients were dropped out because their cycles canceled due to agonist trigger, ovarian hyper-stimulation syndrome (OHSS) or freezing because of OHSS risk. From the remaining 222 patients, 106 participants were allocated in Intravenous lipid (SMOFlipid®) group, whereas 116 who had received short antagonist IVF protocol without intralipid therapy were assigned to control group. Intralipid treatment has been used in our center for appropriate RIF patients since 2016. At the same time, ethical approval was obtained from the local ethics committee. All included participants were informed about the study and gave written consent before data was collected.

All of the women underwent ovulation induction with short antagonist protocol based on their age, BMI, previous cycle response and hormonal conditions on the discretion of the clinician. Intravenous lipid group received intralipid 20% (SMOFlipid®) infusion therapy in addition to antagonist protocol on the day of embryo transfer, day of positive pregnancy test, and continued weekly until the tenth week of gestation when the luteal-placental shift was occurred. The intralipid was given within hours with close monitoring for signs of any allergic reaction. The lipid profile and liver function tests of all patients were normal prior to intralipid administration.

Primary outcomes were implantation rate (number of gestational sacs implanted per total number of embryos transferred), biochemical pregnancy rate (bhcg>/-100 IU at the day of 14 after embryo transfer), clinical pregnancy rate (presence of gestational sac with fetal cardiac activity) and live birth rate (delivery of live infant after 24 weeks of gestation).

Statistical analyses were completed by using SPSS 20.0 (SPSS, Chicago, IL) program. Categorical variables were expressed as frequencies and percentages and analyzed using chi-square tests. Continuous variables were presented as the mean ± standard deviation and analyzed with student independent t-tests. p value lower than 0.05 was considered as statistically significant.

Results

A total of 222 patients were enrolled in the study; 106 patients were allocated in intralipid therapy receiving group whereas 116 patients were in control group. There was not any side effect recorded due to (SMOFlipid®) in the intralipid group. When the demographic variables were investigated age of the patients and number of patients with at least one previous live birth were higher (p=0.003, p=0.001, respectively) and duration of infertility was shorter (p<0.001) in intralipid group. (32.9 vs. 31.03; 17 vs. 4; 4.5 vs. 7.9, respectively) (Table 1).

Table 1. Demographic data

	Intravenous lipid group (n=106)	Control group (n=116)	p
Age (mean ± SD)	32.9 ± 5.7	31.03 ± 3.4	0.003
BMI (mean ± SD)	25.1 ± 4.3	24.4 ± 3.3	0.172
Number of patients with previous biochemical loss	1 (0.9%)	3 (2.5%)	0.362
Number of patients with at least one previous live birth (%)	17 (16.1%)	4 (3.4%)	0.001
Number of patients with recurrent miscarriages (%)	13 (12.2%)	12 (10.3%)	0.654
Number of patients with prior ectopic pregnancy (%)	4 (3.7%)	8 (6.8%)	0.305
Tobacco use	2 (1.8%)	8 (6.8%)	0.071
Duration of Infertility (years) (mean ± SD)	4.5 ± 3.4	7.9 ± 3.6	<0.001

When the endometrial thickness on the day of trigger was compared between two groups, endometrium was found to be thinner in the intravenous lipid group (p<0.001). The total number of transferred embryos was higher in the intravenous lipid group (182 vs. 149). There was not any statistically significant difference in terms of total dosage of gonadotropin, number of retrieved cumulus oophorous complexes, number of M2 oocytes, number of embryos which were suitable for freezing (p>0.05) (Table 2).

Table 2. In vitro fertilization cycle characteristics

	Intravenous lipid group (n=106)	Control group (n=116)	P
Total gonadotropin dose (IU) (mean ± SD)	2646 ± 804	2491 ± 809	0.154
Endometrial thickness at the day of trigger (mm) (mean ± SD)	9 ± 1	10.2 ± 1.1	<0.001
Number of retrieved cumulus oophorous complex (mean ± SD)	11.7 ± 8.3	9.1 ± 5.8	0.007
M2 oocytes (mean ± SD)	6.4 ± 3.5	6.5 ± 3.8	0.839
Number of transferred embryos	182	149	
Cases who have available embryo for freezing	32 (30.1%)	21 (18.1%)	0.037

The number of patients with positive pregnancy test clinical pregnancy rate and live birth rate were statistically significantly higher (p<0.001) in the intravenous lipid group (50.9% vs. 22.4%, 41.5% vs. 19.8%, 29.2% vs. 10.3%, respectively). There was no statistically significant difference between the groups in terms of implantation, spontaneous abortion, multiple pregnancy and chemical pregnancy rates (p>0.05) (Table 3).

Table 3. Pregnancy outcomes

	Intravenous lipid group (n=106)	Control group (n=116)	p
Implantation rate	26%	16%	0.067
Positive pregnancy test	54 (50.9%)	26 (22.4%)	<0.001
Chemical pregnancy	10 (9.4%)	3 (2.5%)	0.029
Clinical pregnancy	44 (41.5%)	23 (19.8%)	<0.001
Spontaneous abortion	13 (12.2%)	11 (9.4%)	0.501
Live birth rate	31 (29.2%)	12 (10.3%)	<0.001
Multiple pregnancy	4 (3.7%)	1 (0.8%)	0.141
Chemical pregnancy rate in positive pregnancy tests	18.5%	11.5%	0.144

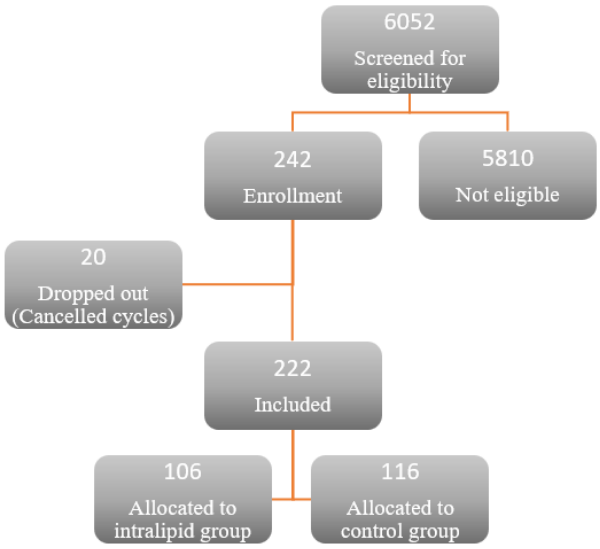

Figure 1. Flow chart of the participants

Discussion

This study revealed that intravenous lipid therapy has a significant effect on better pregnancy outcomes in patients with unexplained RIF undergoing IVF/ICSI. Compared to patients undergo standard IVF protocol, positive pregnancy test, clinical pregnancy rate and live birth rate were higher in intralipid receiving patients.

Although immunomodulation in IVF patients has emerged as an additional treatment in recent years, the exact mechanism by which intravenous lipid is acting is still unclear.[14-15] Uterine natural killer (uNK) cells are one of the critical immune cells involved in the implantation stage,[16] and in the literature, there are many studies about association between uNK and RIF.[17] As immune modulatory agents both immunoglobulin and intralipid can prevent immunological attacks that can cause implantation failure. However, in the literature there is no difference in pregnancy outcomes among women with RIF who received IVIG or intralipid, making intralipid

a more attractive option due to its low cost. In a study of Allahbadia et al., it is proved that intravenous lipids suppress NK cytotoxicity in vitro studies.[18] In the study of Ledee et al., they focused on intravenous lipid treatment due to its immunosuppressive effect on natural killer (NK) cells, in patients with unexplained RIF undergoing IVF/ICSI and showed that the live birth rate was increased at the next embryo transfer.[19]

In the literature, there are a few randomized controlled studies about using intravenous lipid therapy in IVF treatment.[12,20] In a recent randomized controlled research, among patients with prior implantation failure higher pregnancy rate, implantation rate and take home baby rate was found in women who received intralipid.[12] However, primary infertile patients with at least one implantation failure, in which the population did not meet current RIF definitions, were included in this study.[12] In our study, we included primary infertile patients with at least two failed IVF cycles despite quality embryo transfer in accordance with the RIF definition.

A cochrane systematic review on immune therapies for women with unsuccessful implantation suggested that intralipid therapy increases live birth rate in comparison to patients with no additional treatment.[21] On the contrary, a retrospective study demonstrated 43.3% positive pregnancy test rate among patients receiving intralipid treatment, which was not statistically significant.[22] Similarly, early outcomes of a case-control study showed no better pregnancy outcomes among intralipid group over control group.[23]

Dakhly et al., evaluated the effect of intravenous lipid therapy in patients of recurrent spontaneous abortion with increased NK cells activity, and showed an increased rate of ongoing pregnancy and live birth.[20] The superiority of this study to other studies is it was conducted among patients with elevated levels of NK.[20] In our study patients did not underwent any laboratory tests to identify immun dysfunction so it could not clarified whether the benefit of intralipid treatment can be generalized to all patients or to those only with immun dysfunction. Since this is a limitation of our study, we suggest that the immunological biomarker status of patients should be taken into consideration in future studies on this subject. The other limitation of the study was its retrospective design.

Intravenous lipid treatment is suggested to improve pregnancy outcomes of patients with RIF. Nevertheless, when comparing women with or without intralipid therapy, in subsequent studies immunological tests should be performed to show the benefits of treatment more clearly. Further better powered, prospective randomized controlled studies with larger series are needed to evaluate its efficacy or usage as a therapeutic agent for RIF patients.

Compliance with Ethical Standards

This study was approved by Alanya Alaaddin Keykubat University, Health Sciences Scientific Research and Publication Ethics Committee (Decision number: 03/09, Date: 07.07.2022)

Conflict of Interest

The authors have no conflicts of interest relevant to this article.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

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