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The Effect of Fat Emulsion Intralipid 20% in Reproductive Outcome for Patients With Multiple Implantation Failure

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Abstract

Objectives: The aim of this study is to evaluate the effect of fat emulsion intralipid 20% on reproductive outcome of patients with multiple implantation failure (MIF).

Materials and Methods: A retrospective study of 30 women with MIF who received intralipid 20% with in vitro fertilization, intracytoplasmic sperm injection (IVF-ICSI). The treatment cycle was conducted in reproductive endocrine and infertility medicine department (REIMD) at Women Specialized Hospital, King Fahad Medical City (KFMC), from January 2015 to December 2016.

Results: Thirteen of 30 women (43.3%) had a positive pregnancy test and 17 (56.7%) did not. Pregnancy rate showed no statistically significant difference with the use of long protocol in comparison to short antagonist protocol. Use of intralipid 20% did not affect the embryo grading or yield the higher number of frozen embryos.

Conclusions: MIF is a challenging situation in reproductive medicine. Intralipid 20% might be an effective treatment for patients with MIF.

Keywords: Fat emulsion, Intracytoplasmic intralipid, Multiple implantation failure, Pregnancy rate, Sperm injection rate.

Introduction

Multiple implantation failure (MIF) is described as implantation failure in spite of transferring good quality embryos following several in vitro fertilization (IVF) treatment cycles (1). Implantation is a complicated process that requires healthy embryos with receptive endometrium. Many factors can lead to implantation failure due to either maternal or embryonic factors. Uterine anatomy, thrombophilia, immunological factors, and a non-receptive endometrium are amongst the maternal factors and genetic or lab related are amongst the embryonic factors (1).

The patient with repeated implantation failure is a challenge for the infertility specialists. Age remains the most important variable influencing outcome in assisted reproduction (2-4). Advanced maternal age manifests its effects on the clinical in vitro fertilization embryo transfer (IVF-ET) procedure that is due to the variable effects on the pattern of ovarian response and on the reduction of implantation efficiency and due to an increased spontaneous abortion rate (2-4).

Impaired uterine receptivity leads to implantation failure in assisted reproduction (2-4). Thrombophilia and abnormal immunological response could result in a non-receptive endometrium (2-4) and eventually in implantation failure.

Investigation about recurrent implantation failure includes tests for inherited and acquired thrombophilias and with immunological causes. Management should be individualized according to the different etiologies and empirical treatments with low molecular weight heparin (LMWH). Aspirin or corticosteroids are not effective for women with RIF whose test results are negative in thrombophilic tests (2-4). If leukocyte antigen dissimilarity is proven immunologically, treatment with intravenous immunoglobulin (IVIG) might be helpful; however, treatment with intralipid infusion in the presence of increased natural killer cytotoxic activity could be helpful too but is still controversial. Data supporting this practice is conflicting.

The suggested therapy in recurrent implantation failure is intralipid, which is a fat emulsion containing soybean oil, glycerin, egg phospholipids, glycerol, and water. It provides essential fatty acids, linoleic acid, omega-3 and 6 fatty acids, and alpha-linolenic acid (5). Intralipid suppresses natural killer cell activity (NKa) is similar to the effect of IVIG (5).

Intralipid is a milky solution, originally used to provide energy to the patients who could not eat (6) and it is made of purified soybean oil and egg phospholipids. Intralipid has been initially used for parenteral nutrition in patients who are unable to take food orally (6). The mechanism of

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action of the parenteral fat emulsions is the accumulation in macrophages and impairment of their various functions (6). Although the exact immune mechanism by which intralipid acts is not clear, the soybean oil may be the active component that inhibits pro-inflammatory mediators, specifically type 1 T-helper cells (7).

Kalfarentzos et al studied the differences between fat emulsions, intralipid 10%, and intralipid 30% and compared the resulting plasma levels of different lipid components. There were no differences between them. However, intralipid 30% had more lipid components in comparison to intralipid 10%. The fat emulsion with greater concentration of triglyceride has been found to be safe and is used for sick patients requiring total parenteral nutrition (7).

Imbalance of the immune system during implantation or pregnancy may lead to implantation failure or miscarriage and therefore the usage of immunosuppressive or immunomodulatory agents can prevent immunological occurrence (6).

Intralipids have immunosuppressive effects (6) and thus the intravenous intralipid injection affects the proliferation and function of immune cells including the lymphocytes (8) and by inhibiting the IL-2, it decreases the activation signals for T and B lymphocyte (9).

When used in ICSI cycles with patients with RIF, intravenous intralipid 20% infusion improves the clinical pregnancy, the implantation, and the live birth rate (10).

MIF is a distressing condition affecting couples. Immunotherapeutic agents such as immunomodulators and immunosuppressive are new factors but they have been used for managing patients with MIF and have been found to eliminate the damaging reactions against the fetus (8,9). Few studies have been conducted to assess intralipid use in patients undergoing assisted reproductive technologies (ART).

The aim of this study is to evaluate the effect of fat emulsion intralipid 20% on reproductive outcomes of patients with MIF undergoing ART.

Materials and Methods

Thirty women with MIF participated in this study. They were at reproductive endocrine and infertility medicine department (REIMD) at women specialized hospital, King Fahad Medical City (KFMC) from January 2015 to December 2016. All charts of women with 3 or more unsuccessful IVF cycles who received 20% intralipid fat emulsion, age less than 45, and normal uterine cavity were reviewed. The charts were excluded from our analysis if any of the following conditions were recorded in the chart: a patient with medical condition contraindicating the use of intralipid infusion, uterine fibroid, endometrial polyp, endometriosis and hydrosalpinx, intrauterine adhesion and uterine anomalies, deficiency of protein C, protein S, factor V Leiden, antiphospholipid syndrome (lupus anticoagulant), anticardiolipin antibodies (immunoglobulin G or M) [IgG or IgM]), and other recognized thrombophilic conditions.

Statistical Analysis

MS Excel 2010 and SPSS 22.0 software were used for data analysis. Categorical variables were expressed as frequencies and percentages and were analyzed using chi-square tests. Metric data was presented as the mean, +/- standard deviation, and analyzed using independent sample *t* tests. All statistical tests were 2-tailed. The hypotheses were tested based on the *P* value, where *P* less than 0.05 was considered as statistically significant.

Results

Thirty patients were included in the study, 27 of them underwent IVF -ICSI cycle and 3 underwent frozen embryo transfer (FET) cycles. The latter was evaluated for the effect of administration of intravenous intralipid on pregnancy outcome.

Patient demographics and clinical characteristics were demonstrated in Table 1. The identified causes of infertility were tubal factor in (16.7%, n = 5), polycystic ovary (PCO)

Table 1. Basic Demographic and Clinical Characteristics of the Patients (n = 30)

Variables	Characteristics	No. (%)
Female occupation	House wife	26 (86.7)
	Professionals	4 (13.3)
Husband occupation	Employed	10 (33.3)
	Unemployed	20 (66.7)
Hysteroscopy finding	Yes	17 (56.7)
	No	13 (43.3)
RIF	≥3 (Yes)	30(100)
	< 3 (No)	0 (0)
HSG findings	Normal	13 (43.3)
	Bilateral block	5 (16.7)
	Unilateral block	12 (40.0)
Diagnosis	Tubal	5 (16.7)
	PCOS	4 (13.3)
	Male	10(33.3)
	Anovulatory	2 (6.6)
	Unexplaned	4 (13.3)
	Multiple	4(13.3)
	Other	1 (3.3)
PCO	Yes	4 (13.3)
	No	26 (86.7)
Male factor	Yes	10 (33.3)
	No	20 (66.7)
Protocol	Antagonist	21 (70.0)
	Long	6 (20.0)
	FET	3 (10.0)
Drug	Cetrotide	21 (70.0)
	Lupron	5 (16.7)
	Estradiol valerate	3 (10.0)
	GnRH agonist (Decapeptyl)	1 (3.3)
Total AFC	≤3	0 (0.0)
	4-8	9 (30.0)
	9-12	5 (16.7)
	>12	16 (53.3)

Table 1. Continued

Stimulation drug	Gonal F (r-FSH)	12 (40.0)
	Merional (HMG)	7 (23.3)
	Gonal F and lutropin alpha (luveris)	8 (26.7)
	Estradiol valerate	3 (10.0)
Therapy pattern	Gonal F (r-FSH)	12 (40.0)
	Merional (HMG)	7 (23.3)
	Combined therapy (GonalF + HMG)	8 (26.7)
	Frozen embryos	3 (10.0)
Trigger drug	HCG (Pregnyl)	27 (90.0)
	Other	0 (0.0)
	FET	3 (10.0)
Range of mature oocytes (MII)	<3 (MII not good for pregnancy)	9 (30.0)
	≥3 (MII good for pregnancy)	21 (70.0)
Grades	G1	12 (40.0)
	G2	7 (23.3)
	G3	1 (3.3)
	G1 + G2	10 (33.3)
Frozen embryos	≤2	23 (76.7)
	> 2	7 (23.3)
Range of the number of embryo transfers	1	6 (20.0)
	2	24 (80.0)
Range sperm count	≤15 million (oligospermia)	6 (20.0)
	>15 million (normal)	24 (80.0)
Motility range	<32%	8 (26.7)
	≥32%	22 (73.3)
Morphology range	<4%	6 (20.0)
	≥4%	24 (80.0)
Outcome	Non-pregnant	17 (56.7)
	Pregnant	13 (43.3)

RIF, repeated implantation failure; HSG, hysterosalpingogram; PCO, polycystic ovaries; AFC, antral follicle count; PCOS, Polycystic Ovarian Syndrome.

(13.3%, n = 4), male (33.3%, n = 10), anovulatory (6.6 %, n = 2), unexplained (13.3%, n = 4), multiple (13.3, n = 4), and other ones such as endometriosis and fibroid (3.3%, n = 1). Six patients started with long protocol, 21 of them with antagonist protocol, and 3 with FET cycle. Higher pregnancy rate was found with the use of long protocol in comparison to the short antagonist protocol. Use of intralipid 20% did not affect embryo grading or yield higher number of frozen embryos.

Table 2 shows the descriptive analysis and laboratory testing of study parameters. Median age for wife was 37 years which ranges from 31 to45 years, median age of husband was 40 years within the range of 31-60 years, and median duration of infertility was 8 years ranges from 3 to18 years. Median follicle-stimulating hormone (FSH) level was 5.72 IU/L, luteinizing hormone (LH) level was 6.35 IU/L, prolactin level was 254 mIU/L, and thyroid stimulating hormone (TSH) level was 2.23 mIU/L. The median body mass index (BMI) of patients was 29.1 kg/m^2.

Table 3 demonstrates the impact and association of the parameters with pregnancy outcomes.

Table 4 demonstrates the pregnancy rate in the agonist group 4 (66.7%)] and in the antagonist group (8 [33.1%]) with no statistical significance. Applying intralipid 20% did not affect the embryo grading or yield higher number of frozen embryos.

Pregnancy rate with the use of intralipid intravenous infusion was achieved in 43.3% of the patients and 56.6% did not get pregnant. There was no significant statistical difference in pregnancy outcome in relation to measured hormonal profiles (Table 4).

Discussion

The infusion of 20% intralipid solution has been studied with results showing better outcomes in women with RIF (5). In a non-randomized trial on patients with MIF who had an elevated T helper-1 (TH1) cytokine, a 50% pregnancy rate and 46% clinical pregnancy rate were reported (5). The intralipid infusion was given between days 4 and 9 of the ovarian stimulation and was re-given within 7 days of a positive pregnancy test. However, the beneficial effects of the infusion, have shown to be decreased with further treatment cycles. The most amount of reduction in clinical pregnancy rates was obvious in the third IVF treatment cycle and hence immunological tests should be considered in those cases (6).

Clark in 1994 concluded that in a clinical trial intralipid had been successful in treating patients with recurrent miscarriages. It was found that both IVIG and intralipid could suppress NK cell cytotoxicity with equal efficacy in a in vitro assay that made the intralipid a cost-effective option (11). In a more recent study that was published in 2013, impaired endometrial receptivity was assessed and the beneficial effect of intralipid infusion in the presence of increased natural killer cell cytotoxic activity in patients with recurrent implantation failure was identified (12).

Another study showed intralipid suppresses in vivo abnormal NK-cell functional activity and implied that Intralipid can modulate abnormal NK activity in women with reproductive failure (10). In 2016, Abdolmohammadi-Vahid et al recommended the use of immunosuppressive or immunomodulator agents since the imbalance of the immune system during implantation or pregnancy may lead to implantation failure or miscarriage (13). Thus using intralipid with its inhibitory immunological effect may improve pregnancy outcomes (13).

In our study pregnancy rate with the use of intralipid infusion showed no statistical significance between both groups.

Other studies in the literature have shown no difference in reproductive outcomes in women with recurrent implantation failure who received intravenous immunoglobulin or intralipid. One of them is a case-control study that was terminated because of their initial data that reported no pregnancies among the intralipid group compared to untreated control group (14). Many

Table 2. Descriptive Analysis, Laboratory Testing of Study Parameters

	Minimum	Maximum	Median	Mean ± S.D
Female age	31.00	45.00	37.0000	36.5 ± 0.65
Husband age	31	60	40.00	40.9 ± 1.06
Years of infertility	3.00	18.00	8.0000	9.13 ± 0.85
FSH	1	18	5.72	6.57 ± 0.62
LH	2.00	18.00	6.3500	6.88 ± 0.58
Estradiol	33.47	771.00	183.5000	216.31 ± 28.16
Prolactin	1.32	731.20	254.0000	277.96 ± 30.55
Thyroid stimulating hormone (TSH)	.01	21.04	2.2350	2.98 ± 0.68
T4	10.90	23.20	14.9000	15.14 ± 0.49
Vitamin D	9.30	110.40	24.6950	39.96 ± 5.94
Body mass index (BMI)	20.70	37.70	29.1000	29.24 ± 0.76
Dose follicle stimulating hormone (r-FSH) (IU)	112.5	450	168.75	167.5 ± 26.47
Dose of human menopausal gonadotropins (HMG) (mg)	75	450	37.50	92.5 ± 20.24
Total Dose (r-FSH) (IU)	1025.00	4050.00	1725.0000	1611.67 ± 251.1
Total Dose (HMG) (IU)	825	6300.00	412.5000	955 ± 246.76
Sperm Count(million)	0.75	435.00	115.0000	126.28 ± 20.87
B-Human Chorionic Gonadotropin (B-HCG) Test Results	0.00	3627.00	2.0700	193.66 ± 122.15

Table 3. Impact and Association Among Pregnancy Outcome and Other Parameters

		Non-Pregnant No. (%)	Pregnant No. (%)	OR [95% CI]	*P* Value
Hysteroscopy finding	Yes	10 (58.8)	7 (53.8)	1.22 [0.285 - 5.255]	0.785
	No	7 (41.2)	6 (46.2)		
Hysterosalpingogram findings	Normal	8 (47.1)	5 (38.5)	1.42 [0.328 - 6.174]	0.638
	Bilateral block	4 (23.5)	1 (7.7)	3.69 [0.36 - 37.858]	0.249
	Unilateral block	5 (29.4)	7 (53.8)	0.36 [0.079 - 1.615]	0.176
Polycystic ovaries	Yes	1 (5.9)	3 (23.1)	0.21 [0.019 - 2.29]	0.170
	No	16 (94.1)	10 (76.9)		
Male factor	Yes	5 (29.4)	5 (38.5)	0.67 [0.145 - 3.075]	0.602
	No	12 (70.6)	8 (61.5)		
Protocol	Antagonist	13 (76.5)	8 (61.5)	2.03 [0.417 - 9.887]	0.376
	Long	2 (11.8)	4 (30.8)	0.3 [0.045 - 1.982]	0.197
	Frozen embryo transfer	2 (11.8)	1 (7.7)	1.6 [0.129 - 19.839]	0.713
Drugs	GnRH antagonist-Cetrolix (Cetrotide)	13 (76.5)	8 (61.5)	2.03 [0.417 - 9.887]	0.376
	Leuprolide	2 (11.8)	3 (23.1)	0.44 [0.063 - 3.155]	0.410
	Estradiol Valerate	2 (11.8)	1 (7.7)	1.6 [0.129 - 19.839]	0.713
	GnRH agonist (Decapeptyl)	0 (0.0)	1 (7.7)	0.35 [0.011 - 11.392]	0.245
Antral follicular count (AFC)	4-8	6 (35.3)	3 (23.1)	1.82 [0.357 - 9.272]	0.469
	9-12	2 (11.8)	3 (23.1)	0.44 [0.063 - 3.155]	0.410
	>12	9 (52.9)	7 (53.8)	0.96 [0.227 - 4.102]	0.961
Stimulation drug	r-Follicle Stimulating Hormone (r-FSH)	7 (41.2)	5 (38.5)	1.12 [0.256 - 4.905]	0.880
	Human menopausal gonadotropins (HMG)	5 (29.4)	2 (15.4)	2.29 [0.367 - 14.323]	0.368
	r-FSH and Lutropin alpha	3 (17.6)	5 (38.5)	0.34 [0.064 - 1.829]	0.201
	Estradiol valerate	2 (11.8)	1 (7.7)	1.6 [0.129 - 19.839]	0.713
Therapy pattern	r-Follicle stimulating hormone (r-FSH)	7 (41.2)	5 (38.5)	1.12 [0.256 - 4.905]	0.880
	Human menopausal gonadotropins (HMG)	5 (29.4)	2 (15.4)	2.29 [0.367 - 14.323]	0.368
	Combined Therapy (r-FSH + HMG)	3 (17.6)	5 (38.5)	0.34 [0.064 - 1.829]	0.201
	Forzen embryos	2 (11.8)	1 (7.7)	1.6 [0.129 - 19.839]	0.713
Trigger drug	Human chorionic gonadotropins (HCG-Pregnyl)	15 (88.2)	12 (92.3)	0.63 [0.05 - 7.75]	0.713
	Frozen embryo transfer (FET)	2 (11.8)	1 (7.7)		

Table 3. Continued

Mature oocytes (MII)	<3 (MII not good for pregnancy)	6 (35.3)	3 (23.1)	1.82 [0.357 - 9.272]	0.469
	≥3 (MII good for pregnancy)	11 (64.7)	10 (76.9)		
Embryo grades	G1	6 (35.3)	6 (46.2)	0.64 [0.145 - 2.784]	0.547
	G2	5 (29.4)	2 (15.4)	2.29 [0.367 - 14.323]	0.368
	G3	1 (5.9)	0 (0.0)	1.63 [0.05 - 52.369]	0.374
	G1 + G2	5 (29.4)	5 (38.5)	0.67 [0.145 - 3.075]	0.602
Frozen embryos	≤2	13 (76.5)	10 (76.9)	0.98 [0.177 - 5.385]	0.997
	> 2	4 (23.5)	3 (23.1)		
Number of embryo transfers	1	3 (17.6)	3 (23.1)	0.71 [0.119 - 4.297]	0.713
	2	14 (82.4)	10 (76.9)		
Sperm count	≤15 million (Oligospermia)	1 (5.9)	7 (53.8)	0.05 [0.005 - 0.532]	*0.003
	> 15 million (Normal)	16 (94.1)	6 (46.2)		
Motility range	< 32%	4 (23.5)	4 (30.8)	0.69 [0.136 - 3.519]	0.657
	≥32%	13 (76.5)	9 (69.2)		
Morphology range	< 4%	3 (17.6)	3 (23.1)	0.71 [0.119 - 4.297]	0.713
	≥4%	14 (82.4)	10 (76.9)		

Table 4. Relationship Between Laboratory Test Among Pregnancy Outcome

		Non-Pregnant No. (%)	Pregnant No. (%)	OR [95% CI]	*P* Value
Follicular stimulating hormone (FSH), IU/L	Abnormal	1 (5.9)	2 (15.4)	0.34 [0.028 - 4.273]	0.390
	Normal	16 (94.1)	11 (84.6)		
Luteinizing hormone (LH), IU/L	Abnormal	0 (0.0)	1 (7.7)	0.35 [0.011 - 11.392]	0.554
	Normal	17 (100.0)	12 (92.3)		
Estradiol, pg/mL	Abnormal	7 (41.2)	5 (38.5)	1.12 [0.256 - 4.905]	0.880
	Normal	10 (58.8)	8 (61.5)		
Prolactin, mIU/L	Abnormal	9 (52.9)	3 (25.0)	3.75 [0.754 - 18.642]	0.098
	Normal	8 (47.1)	9 (75.0)		
Thyroid stimulating hormone (TSH), mIU/L	Abnormal	3 (17.6)	4 (30.8)	0.48 [0.087 - 2.68]	0.400
	Normal	14 (82.4)	9 (69.2)		
T4, ug/dL	Abnormal	0 (0.0)	3 (25.0)	0.1 [0.004 - 2.164]	0.089
	Normal	17 (100.0)	9 (75.0)		
Vitamin D, ng/mL	Abnormal	14 (87.5)	8 (80.0)	2.92 [0.547 - 15.561]	0.201
	Normal	2 (12.5)	2 (20.0)		

have recommended the need for larger randomized controlled trials to prove the efficacy of intralipid before it can be recommended for routine use. In 2016, Dakhly et al demonstrated that Intralipid administration did not increase the frequency of chemical pregnancy (15). However, they recommended that findings related to ongoing pregnancy and live birth should be investigated further (15). They also defined the use of intralipid as a valuable therapy and advised that its use should be based solely on randomized controlled trial (16).

Needless to say, the present study is not without limitations. The main limitations are the small sample size, lack of the control group, and the retrospective study design.

A randomized controlled study with a larger number of patients is needed. More conclusive evidence in terms of the best dose and timing of intralipid for the patients with MIF is also required.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the institutional review board (IRB) of KFMC prior to starting (IRB 16-440, 08/12/2016).

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