



The Effect of Fat Emulsion Intralipid Infusion on Reproductive Outcome for Women with Unexplained First Trimester Habitual Abortion

Eltahera M. Goda ^{a*}, Sherif I. Shuwaikh ^a, Walid M. Ata Allah ^a
and Safaa K. Maray ^a

^a *Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Egypt.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objectives: To study the effect of the use of intralipid in management of women suffering from unexplained first trimester habitual abortion.

Methods: The study was a prospective cohort study, which conducted in Tanta university Hospital; Egypt. It included 93 women with history of two or more unexplained recurrent abortion in the first trimester. They were divided into three groups: group I received only intralipid, group II received low molecular weight heparin (LMWH) and low dose aspirin, and group III served as controls and received only saline as placebo. The patients were followed up until continuation of pregnancy into the second trimester. Occurrence of complication and pregnancy outcomes were evaluated.

Results: Ninety three women were included. After treatment, more pregnancy continued into the second trimester, more live births and less numbers of abortions in group A and B in comparison with group C (p=0.008, 0.008 and 0.035) respectively. Maternal and neonatal outcomes were comparable in all studied regimens.

Conclusions: Management of women with unexplained first trimester habitual abortion (before 14 weeks) with intralipid or LMWH with small dose of aspirin may increase the proportion of pregnancy continued into the second trimester, more live births and less numbers of abortions. However, LMWH is more superior to the intralipid but with more side effect.

Keywords: *Intralipid infusion; low molecular weight heparin; unexplained first trimester habitual abortion.*

1. INTRODUCTION

Recurrent spontaneous abortion (RSA) is defined as ≥ 3 consecutive miscarriages before the 20th week of gestation [1]. RSA does affect 0.5-1% of couples [2]. The percentage of recurrent pregnancy losses are approximately 24% after two clinical pregnancy losses. Thus some authors prefer to investigate patients with two consecutive abortions [3].

Known causes of RSA are genetic abnormalities, structural uterine abnormality, autoimmunity, [4] chromosomal abnormalities, maternal thrombophilic disorder, and endocrine abnormalities [polycystic ovary syndrome (PCOs), hyperprolactinemia, luteal phase defect. The unexplained causes of RSA have been stated to represent 50% of cases of RSA [5].

After implantation, the endometrium (decidua) is infiltrated by trophoblast cells of fetal origin. In order for a trophoblast to penetrate, the decidua has a unique set of immune cells with specific characteristics including: the decidual macrophage and regulatory cell (Treg) show augmented suppressive profile in the decidua. The immune factors behind RSA are complicated. In addition to autoimmune diseases, imbalances between Treg cells, helper T (Th17) cells and cells that are called Natural killer (NK) play a key role in RSA [6]. Uterine NK cells (uNK) seen with decidualization and implantation processes are due to endocrinal signals that mobilize uNK cell from spleen into uterus in the human decidua during first trimester, decline after that, absent at term [6].

Interaction between uNK cells /trophoblast result in production of cytokines (tumor necrosis factor, interferone- γ), there are two hypotheses to explain how uNK cells lead to RSA either by being hostile to invade trophoblast, or by facilitating implantation of blastocysts that are abnormal causing RSA [7].

Investigations of uNK cells show controversial results, NK cell with CD16 expression or CD56 expression or both, there is no clear evidence that peripheral killer cells can cause RSA. Therefore, testing for peripheral LNK as a marker of events at RAS is inappropriate and should not be offered routinely in investigation of couples suffering from RSA [8]. However, there is no

proven immunological mechanism linked to RSA, consequently many immune therapies tried to improve outcome of pregnancy [9].

Intralipid is suggested one, a fat emulsion containing egg phospholipids, soybean oil and glycerin [10]. Although the way that intralipid suppress the immunity still unknown, active component of intralipid inhibits pro- inflammatory mediators specifically T-helper cells, so enhance implantation [11].

Other therapies involve utilization of low molecular weight heparin [12]. LMWH exerts anti-inflammatory action that counteracts the pro-inflammatory response. LMWH may participate in organizing pregnancy processes at fetal-maternal interface like inhibition of trophoblast apoptosis and encouragement of Trophoblast invasiveness [13]. So, the aim of our study was to compare the efficacy and safety of both regimens in the management of unexplained first trimester habitual abortion.

2. PATIENTS AND METHODS

The study was conducted at Tanta Woman's Health Hospital; Egypt from 2019 to 2020. Eligible participants: We included women with ages of < 35 years old and with a history of two or more unexplained recurrent abortion in their second half of the first trimester, where the rate of miscarriage seems to be rare about (2–4%) and to decrease the risk of chromosomal abnormality. The exclusion criteria were women with history of Antiphospholipid Syndrome (APS) or other thrombophilic condition, any endocrinal disorders as (hyperprolactinemia, PCOs and thyroid disease), diabetes mellitus, chronic hypertension, any congenital anomalies presenting in previous offspring, liver and kidney diseases, obese women (BMI > 30), smoking and alcohol consumption, multiple pregnancy, uterine cavity abnormalities, women with any chromosomal abnormalities. Women with any hypersensitivity reactions to intralipid, and women refused to participate in the study were also excluded. Women who met the inclusion criteria were subjected to detailed history including, obstetric history (especially, numbers of recurrent abortion, gestational age of each miscarriage and the methods to terminate either surgical or medical or spontaneous) and full general and abdominal examination to exclude

any endocrinal disorders or general metabolic diseases, and baseline investigations including: Rhesus factor (Rh), complete blood count (CBC), post prandial blood sugar, prothrombin time (PT), activated partial thromboplastin time (APTT), thyroid function test, prolactin level, karyotyping for both couples, thrombophilia screening which included (factor V mutation, prothrombin gene mutation, protein C and S deficiency, methylenetetrahydrofolate reductase (MTHFR) gene mutation, hyperhomocysteinemia, presence of lupus anticoagulant, anticardiolipin antibodies), hysterosalpingography and 4D ultrasound. Participants were randomized by computer-generated program into three groups. Group I (n=60) received intralipid infusion by drawing 4-100 ml of 20% intralipid solution into a syringe and adding it into 250 ml of sterile saline. This solution was infused by slow intravenous (IV) infusion over 20-60 minutes without exposure to sun light, with the started rate of infusion not exceeding 1ml/m during the first 10 minutes to observe occurrence of any hypersensitivity reaction, first time between days 4 and 9 of the ovulatory cycle according to the date of her menstrual cycle [14] then 27 women were excluded from the study who did not get pregnant and only 33 women, who got pregnant, those women received intralipid for the second time within 7 days of positive serum pregnancy test [9], and again at week 10 of gestation [15]. Group II received LMWH subcutaneous (SC) injection and low dose aspirin orally daily from the time of the diagnosis of pregnancy till the ending of first trimester. It was given in prophylactic dose of enoxaparin which is 20 mg if the patient's body weight is <50 kg and 40 mg if the patient's body weight ranges between 50 kilograms and 90 kilograms and aspirin 75 mg daily, and Group III (the control group) received saline only as placebo. The follow-up schedule included: Abdominal ultrasound was done every 2 weeks during the first trimester to confirm fetal viability. All women underwent routine antenatal care for detection of any maternal or fetal complications. Ultrasound scan evaluation was done every month to confirm integrity of the pregnancy, to detect any developed congenital anomalies, the rate of fetal growth, and development of amniotic fluid problems. With regard to the study outcomes, there were two primary end points which were the proportion of women who show continuation of their pregnancy in to the second trimester.

Development of antenatal maternal or fetal complication including congenital anomalies, intrauterine growth retardation (IUGR), intrauterine fetal death (IUFD), pre-eclampsia, drug hypersensitivity or other drugs complication. With regard to the sample size, the study enrolled all patients who came to the hospital and had fulfilled the inclusion criteria in the one year study; one hundred and twenty women with history of two or more unexplained recurrent abortions in their first trimester. 60 women in group A received intralipid between days 4 and 9 of their ovulatory cycle according to date of their menstrual cycle, only 33 ladies got pregnant and 27 ladies did not come pregnant, so they were excluded from the study, group B (n=30) and group C (n=30). The net sample size included 93 women.

Statistical Analysis: The data was collected and entered into Microsoft Excel Database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 22). Quantitative variables were described in the form of mean \pm standard deviation and median (range). Qualitative variables were described as number and percent. In order to compare normally distributed quantitative variables between the three studied groups, ANOVA test was performed, Kruskal-Wallis H test was used instead for non- normally distributed quantitative variables. Qualitative variables were compared using χ^2 test or Fisher's exact test when the expected frequency is less than 5. P value < 0.05 is considered significant.

3. RESULTS

Both groups were comparable in baseline socio-demographic data and the patients' investigations without statistically significant differences (Table 1).

There were statistically significant differences between the three studied groups as regard to the fate of current pregnancy with more pregnancy continued in to the second trimester, more live births and less numbers of abortions in group A and B in comparison to group C (P=0.008, 0.008 and 0.035) respectively. And by comparing the fate of current pregnancy among group A and group B only, we found no statistically significant differences between them (P>0.05) (Table 2).

Table 1. Demographic data and investigations of the three studied groups

	Group (A) (n=33)	Group (B) (n=30)	Group (C) (n=30)	p-value
Age				
Min.-Max.	20-35	21-34	20-34	0.812
Mean \pm SD	27.39 \pm 4.55	27.40 \pm 4.37	26.77 \pm 4.26	
BMI(kg/m²)				
Min.-Max.	22.0-30.6	21.5-29.7	23.5-29.9	0.246
Mean \pm SD	25.76 \pm 2.66	25.44 \pm 2.15	26.43 \pm 2.07	
Gravidity				
Min.-Max.	2 – 6	2 – 8	2 – 7	0.947
Median	3	3	3	
Parity				
Min.-Max.	0 – 2	0 – 2	0 – 1	0.497
Median	0	0	0	
Number of Abortions				
Min.-Max.	2 – 6	2 – 8	2 – 7	0.807
Median	3	3	3	
Hemoglobin				
Min.-Max.	10.30-12.50	10.30-12.50	10.30-12.30	0.940
Mean \pm S.D	11.16 \pm 0.65	11.16 \pm 0.68	11.19 \pm 0.58	
PT (S)				
Min.-Max.	9-12	9.0-11.0	9.00-10.0	0.416
Mean \pm S.D	11.64 \pm 0.74	11.588 \pm 0.67	11.53 \pm 0.68	
PTT (S)				
Min.-Max.	25.00-32.00	23.00-35.00	25.00-35.00	0.204
Mean \pm S.D	28.14 \pm 2.12	29.10 \pm 3.19	29.90 \pm 3.59	
TSH				
Min.-Max.	0.40-4.00	0.70-3.70	0.40-4.00	0.314
Mean \pm S.D	2.36 \pm 1.21	2.22 \pm 0.86	2.07 \pm 0.96	
Prolactin level				
Min.-Max.	3-18	5-18	5-22	0.059
Mean \pm S.D	12.45 \pm 3.75	13.65 \pm 3.62	11.57 \pm 3.50	
Postprandial Blood Sugar				
Min.-Max.	80-135	76-135	99-134	0.757
Mean \pm S.D	109.24 \pm 13.38	110.43 \pm 16.49	108.77 \pm 7.99	
Protein C				
Min.-Max.	80-134	100-140	70-140	0.436
Mean \pm S.D	115.55 \pm 13.91	118.03 \pm 9.87	111.23 \pm 17.29	
Protein S				
Min.-Max.	60-150	68-148	70-133	0.407
Mean \pm S.D	115.67 \pm 18.26	117.60 \pm 14.50	110.70 \pm 17.93	
Homocysteine				
Min.-Max.	5-10	5-9	5-9	0.402
Mean \pm S.D	7.00 \pm 1.46	6.93 \pm 1.44	7.37 \pm 1.35	
Anti cardioliipin:IgG				
Min.-Max.	5-8	5-8	5-8	0.400
Mean \pm S.D	6.27 \pm 1.07	6.47 \pm 1.14	6.63 \pm 0.96	
Anti cardioliipin:IgM				
Min.-Max.	3-5	3-5	3-5	0.258
Mean \pm S.D	4.15 \pm 0.76	4.00 \pm 0.74	3.83 \pm 0.79	

PT, prothrombine time, PTT, partial thromboplastin time, TSH, thyroid stimulating hormone, anticardiolipin IgG and IgM. Data are presented as mean \pm SD and range. Statistically significant at $p \leq 0.05$.

Group A (n=33): Intralipid. Group B (n=30): LMWH + low dose aspirin; Group C (n=30): Saline as placebo.

Table 2. Comparison between three groups as regard to fate of current pregnancy

Results	Group (A) (n=33)		Group (B) (n=30)		Group (C) (n=30)		p-value*	p-value**
	No.	%	No.	%	No.	%		
Pass to 14 th Weeks	17	51.5	21	70.0	9	30.0	0.008*	0.134
Threatened abortion	6	18.2	8	26.7	2	6.7	0.120	0.418
Had recurrent abortion	16	48.5	9	30.0	21	70.0	0.008*	0.134
Live birth	16	48.5	19	63.3	9	30.0	0.035*	0.236

Data are presented as number (percentage). Statistically significant at $p \leq 0.05$.

P *: comparison between the three studied groups.

P **: comparison between Group A and Group B.

Group A (n=33): Intralipid. Group B (n=30): LMWH + low dose aspirin; Group C (n=30): Saline as placebo.

Table 3. The most common complication in group B who received aspirin and LMWH

Complications	Group B (n=30)	
	N	(%)
Bruising at injection site	18	(60.0)
Bleeding gums	4	(13.3)
Gastrointestinal troubles	3	(10.0)
Epistaxis	2	(6.7)
Transient thrombocytopenia	1	(3.3)

Data are presented as number (percentage). Group B (n=30): LMWH +low dose aspirin

Table 4. Fetal and maternal antenatal and postnatal outcome of three studied groups

Results	Group (A) (n=33)		Group (B) (n=30)		Group (C) (n=30)		p-value
	No.	%	No.	%	No.	%	
Fetal complications							
IUFD	0/17	0.0	2/21	9.5	0/9	0.0	0.670
Preterm labor	1/17	5.9	0/21	0.0	0/9	0.0	0.553
Incubation	4/16	25.0	5/19	26.3	2/9	22.2	1
Congenital anomaly	0/16	0.0	1/19	5.3	1/9	11.1	0.679
Maternal complications							
Preeclampsia	4	12.1	1	3.3	2	6.7	0.496

Data are presented as number (percentage). Statistically significant at $p \leq 0.05$.

Group A (n=33): Intralipid. Group B (n=30): LMWH +low dose aspirin; Group C (n=30): Saline as placebo.

The most common complications of LMWH are summarized in (Table 3). 18 (60%) suffered from bruising at injection site, 4 (13%) suffered from bleeding gums, 3 (10%) developed gastrointestinal troubles; two women developed epistaxis and one case suffered from transient thrombocytopenia.

There was no significant difference between both study groups as regard all fetal and maternal outcomes, including IUFD, IUGR, preterm delivery, incubation, congenital anomaly and the occurrence of preeclampsia ($P > 0.05$) (Table 4).

4. DISCUSSION

The study demonstrated a better pregnancy outcome with Intralipid and LMWH as compared

with the control group in the form of more pregnancy that was continued into the second trimester, more live births and less numbers of abortions. However, LMWH regimen was more superior to Intralipid but this was associated with more side effect.

The results of our study is in agreement with the study of Dakhly et al. [9] who tried intralipid in the treatment of recurrent abortion on 296 women (144 in the intralipid group and 152 in the control group) with spontaneous pregnancy or in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI). Intralipid was given only once, intravenous infusion of 20% intralipid on the day of oocyte retrieval at a dose of 9 mg/mL of the total blood volume. The primary outcome

(chemical pregnancy) was seen in 84 (58.3%) women in the intralipid group, and 76 (50%) in the control group ($P=0.129$). The frequencies of live birth and ongoing pregnancy were the only significant differences in outcomes that was observed between both studied groups ($P=0.005$ for both). In contrast to our study the same author reported that in the intralipid group 18 cases (12.5%) had spontaneous abortion, 54 cases (37.5%) had ongoing pregnancy and 54 cases (37.5%) had live birth, meanwhile in our study we found that regarding the intralipid group 16 patients (49.5%) had spontaneous abortion and 16 patients (48.5%) had live birth (9). This differences may be attributed to the difference in the number of studied patients, dose and sequel of intralipid.

Meng et al. [14] studied the effectiveness of intralipid on patients who suffered from recurrent abortions (76 patients in the intralipid group and 78 patients in the Intravenous immunoglobulin (IVIG) group). Intralipid 20% (250ml) was given on the third day of the menstrual cycle and the injection time was no less than 2 hours. Subsequently, repeated injections were given every 2 weeks before pregnancy and once a week after pregnancy until week 12 of gestation. From the 76 patients in the intralipid group, 17 patients had not been pregnant; eight patients had a repeated spontaneous abortion. The rate of successful pregnancies was 92.1 % (70/76, excluding embryos with abnormal chromosomes) in the intralipid group and 88.2 % (67/76) in the IVIG group ($P=0.415$). There were also no significant differences between two groups before treatment, after treatment and during pregnancy ($P>0.05$). The rate of successful pregnancies was higher in this study more than in our study and this may be attributed to the dose of intralipid repeated every 2 weeks before pregnancy and a week after pregnancy until the end of first trimester and was given earlier than our study in the third day of menstrual cycle. There was no neonatal malformation among the babies in this study like in our study and no side effect in intralipid group.

Also our results were in concordance with the results of Lédée et al. [10] who tried intralipid in the management of unexplained recurrent abortions on 94 patients undergoing IVF. The live birth rate of the RSA treated with Intralipid reached 54% (51/94) at the next embryo transfer.

In contrast to our study, Martini et al., [11] used Intralipid Infusion to improve live birth rates in

patients with recurrent pregnancy loss the use of historical control data and 127 study patients underwent ICSI who received intralipid therapy [4 mL (20%) intralipid solution injected into 250 mL normal saline]. The infusions were administered 7–10 days before embryo transfer or insemination and it was repeated at approximately 6 weeks gestation and again at approximately 10 weeks gestation. And they found that Intralipid administration did not result in a significantly higher number of clinical pregnancies when compared to baseline clinical pregnancy rate in the control population ($P=0.12$). In addition, the intralipid cohort did not have a significantly higher number of live births when compared to the control population ($P=0.80$). This study was limited by its relatively small sample size. Furthermore, a notable limitation in this study was the use of historical control data as opposed to age-matched controls. The majority of patients in this study conceived through IVF with fresh or frozen embryo transfer. There was a small subset of patients that underwent intrauterine insemination who were included due to a diagnosis of recurrent pregnancy loss.

Our study supported by the study of Mekinian et al. [15] who studied the role of different immunomodulation in unexplained recurrent miscarriage and recurrent implantation failure. Intralipids 20% intravenous infusions received once (if natural killer cell<15%) or more (if natural killer cell>15%). In our study we did not investigate the number of natural killer cell, we excluded only other causes of recurrent abortion) Among 200 women with recurrent miscarriages (unexplained $n = 38$) and implantation failure ($n = 162$) and which were treated with intralipids, the pregnancy rate was 52% with pregnancy ongoing/live birth rate of 91%.

In the same study 364 women with at least two pregnancy losses were randomly assigned to 3 groups including those who received: aspirin with LMWH, aspirin alone or placebo. The live birth rate was 69.1% (67/97) in patients who received aspirin with LMWH (like our study), 61.6% (61/99) in patients who received aspirin, ($P=0.04$) [15].

Also the results of our study is in line with the study of Coulam and Acacio, [16] who studied immunotherapy for the treatment of reproductive failure on 200 women experiencing recurrent reproductive failure (162 with a history of recurrent implantation failure and 38 with

spontaneous recurrent pregnancy loss). The pregnancy rate per cycle of treatment with intralipid for women experiencing reproductive failure with elevated NK cell activity was 52%. Of those who became pregnancy, the abortion rate was 9% and live birth/ongoing pregnancy rate was 91%. When the pregnancy outcomes of women with a history of reproductive failure and elevated NK cell cytotoxicity who were treated with intralipid were compared with age and indication matched women treated with IVIg, no significant differences were seen. The overall livebirth/ongoing pregnancy rate per cycle of treatment was 61% for women who were treated with intralipid and 56% for the women who were treated with IVIg.

In agreement with our study, Achilli et al. [17] studied the current evidence on the role of immunotherapy in IVF and in the management of recurrent pregnancy loss (RPL), among 200 women with recurrent pregnancy loss (38 women) and recurrent implantation failure (162 women) and elevated NK cell activity, who were treated with intralipids, the pregnancy rate was 52%. And also the study of Singh et al. [18] who studied the effect of administration of intravenous intralipid on pregnancy outcomes on 105 women with implantation failure after IVF/ICSI; the women in the study arm (n = 52) received 2 doses of 20% intravenous intralipid (4 ml diluted in 250 ml normal saline by slow infusion). The first dose was given immediately after oocyte recovery, and the second dose was given on the day of embryo transfer, 1 h prior to the transfer. There was no significant difference in the baseline characteristics. After that, there was a significant difference in the biochemical pregnancy rate in the intralipid group (40.38%) versus control (16%) (P=0.04), clinical pregnancy rate (34.62% vs 14%), (P=0.006)], and take home baby rate 28.8% vs 10%, (P=0.024)]. No adverse effects of intralipid were observed.

5. CONCLUSION

Management of women with unexplained first trimester habitual abortion (before 14 weeks) with intralipid or LMWH with low dose aspirin may increase the proportion of pregnancy continued into the second trimester, more live births and less numbers of abortions. However, LMWH is more superior to the intralipid but with more side effect. Both regimens are associated with the same maternal and fetal outcomes.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Written consent was obtained from all eligible participants after explaining the nature of the study.

ETHICAL APPROVAL

The protocol of the study was approved by The Tanta University Medical Ethical Review Board.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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