Original Research Article

The effect of fat emulsion intralipid infusion on reproductive outcome for women with unexplained first trimester habitual abortion

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

Methods: The study was a prospective cohort study, 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. 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.

Introduction

Recurrent spontaneous abortion (RSA) is defined as ≥ 3 consecutive miscarriages before 20th week of gestation. **[1]** RSA 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 patient 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), hyperprolactinema, luteal phase defect,…]. The unexplained causes represent 50%. **[5]**

After implantion, the endometrium (decidua) is infiltrated by trophoplast cells of fetal origin. In order for trophoplast to penetrate, the decidua has a unique set of immune cells with specific characteristics, 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 decidalization 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-y), 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 is low molecular weight heparin. **[12]** LMWH exerts anti-inflammatory action that counteracts the pro-inflammatory response. LMWH may be participate in organizing pregnancy processes at fetal-maternal interface like inhibition of trophoblast apoptsis & 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.

Patients and methods

The study was conducted at Tanta Woman's Health Hospital; Egypt from 2019 to 2020. The protocol of the study was approved by The Tanta University Medical Ethical Review Board. Eligible participants: We included women with ages of < 35 years old and with 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 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. Enrollment**:** Written consent was obtained from all eligible participants after explaining the nature of the study. 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 as 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 is infused by slow intravenous (IV) infusion over 20-60 minutes without exposure to sun light, with started rate of infusion not exceed 1ml/m during first 10 minutes to observe occurrence of any hypersensitivity reaction, first time between days 4 and 9 of ovulatory cycle according to date of her menstrual cycle **[14]** then we excluded 27 women from the study (did not get pregnant) and only 33 women (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 diagnosis of pregnancy till ending of first trimester. It was given in prophylactic dose of enoxaparin which is 20 mg if patient's body weight <50 kg and 40 mg if patient's body weight 50–90 kg and aspirin 75 mg daily, and Group III (control) received saline only as placebo. Follow-up schedule" 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 evaluation was done every month to confirm integrity of pregnancy, detect any developed congenital anomalies, rate of fetal growth, and development of amniotic fluid problems. 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 grow retardation (IUGR), intrauterine fetal death (IUFD), pre-eclamsia ,drug hypersensitivity or other drugs complication. Sample size: This study enrolled all patients who came to our hospital and fulfilled our inclusion criteria in a one year study; one hundred twenty women with history of two or more unexplained recurrent abortion in their first trimester. 60 women in group A received intralipid between days 4 and 9 of ovulatory cycle

according to date of her menstrual cycle, only 33 got pregnant and 27 didn't come pregnant, so excluded from the study, group B (n=30) and group C (n=30). The net sample size includes 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 ± standard deviation and median (range). Qualitative variables were described as number and percent. In order to compare normally distributed quantitative variables between 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 $\chi 2$ test or Fisher's exact test when the expected frequency is less than 5. P value < 0.05 is considered significant.

Results

Both groups were comparable in baseline socio-demographic data and patient's investigations without statistically significant differences **(Table1).**

There were statistically significant differences between three studied groups as regard to the fate of current pregnancy with more pregnancy continued in to 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) .**

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

There is 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)**.

Discussion

The study demonstrated a better pregnancy outcome with Intralipid and LMWH as compared with the control group in the form of more pregnancy continued into second trimester, more live births and less numbers of abortions. However, LMWP regimen was more superior to Intralipid but with more side effect.

Our study come in agreement with the study of **Dakhly et al. [9]** who tried intralipid in treatment of recurrent abortion on 296 women (144 in 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. Primary outcome (chemical pregnancy) was seen in 84 (58.3%) women in intralipid group, 76 (50%) in control group (P=0.129). The frequencies of live birth and ongoing pregnancy are 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 intralipid group 18 cases (12.5%) have spontaneous abortion, 54 cases (37.5%) have ongoing pregnancy and 54 cases (37.5%) have live birth, meanwhile in our study we found that regarding the intralipid group 16 (49.5%) have spontaneous abortion and 16 (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 suffered from recurrent abortion (76 patients in intralipid group and 78 patients in 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 2h. Subsequently, repeated injections were given every 2 weeks before pregnancy and once a week after pregnancy until week 12 of gestation. From 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 is higher in this study more than our study may be attributed to 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 were no neonatal malformation among the babies in this study like our study and no side effect in intralipid group.

Also our results were in concordance with **Lédée et al. [10]** who tried intralipid in management of unexplained recurrent abortion 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 contrst to our study, **Martini et al., [11]** used Intralipid Infusion to improve live birth rates in patients with recurrent pregnancy loss using 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 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 received once (if natural killer cell<15%) or more (if natural killer cell>15%). In our study we did not investigate 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: received aspirin with LMWH, aspirin alone or placebo. The live birth rate 69.1% (67/97) in patients received aspirin with LMWH (like our study), 61.6% (61/99) in patients received aspirin, (P=0.04). **[15]**

Also our study is in line with the study of **Coulam and Acacio, [16]** who studied immunotherapy for 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 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 treated with intralipid and 56% 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, 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.

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.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

References

1. Davari-Tanha F, Tehraninejad ES, Ghazi M, Shahraki Z. The role of G-CSF in recurrent implantation failure: A randomized double blind placebo control trial. International Journal of Reproductive BioMedicine. 2016;14(12):737.

2. Wang NF, Kolte AM, Larsen EC, Nielsen HS, Christiansen OB. Immunologic abnormalities, treatments, and recurrent pregnancy loss: what is real and what is not? Clinical obstetrics and gynecology. 2016;59(3):509-23.

3. Zhang L, Yang Y, Zhang R, Luo L, Tan J, Zhou L, et al. Comparison of the etiological constitution of two and three or more recurrent miscarriage. Zhonghua fu Chan ke za zhi. 2018;53(12):855-9.

4. Li X, Zhao J, Liu X. Diagnosis and treatment of antiphospholipid antibody-related recurrent spontaneous abortion and analysis of therapeutic drugs and pregnancy outcome in 75 patients with antiphospholipid syndrome. Beijing da xue xue bao Yi xue ban= Journal of Peking University Health Sciences. 2018;50(6):956-61.

5. Qian J, Zhang N, Lin J, Wang C, Pan X, Chen L, et al. Distinct pattern of Th17/Treg cells in pregnant women with a history of unexplained recurrent spontaneous abortion. Bioscience trends. 2018.

6. Zhao X, Jiang Y, Wang L, Li Z, Li Q, Feng X. Advances in understanding the immune imbalance between T-lymphocyte subsets and NK cells in recurrent spontaneous abortion. Geburtshilfe und Frauenheilkunde. 2018;78(07):677-83.

7. Kamoi M, Fukui A, Kwak-Kim J, Fuchinoue K, Funamizu A, Chiba H, et al. NK 22 Cells in the Uterine Mid-Secretory Endometrium and Peripheral Blood of Women with Recurrent Pregnancy Loss and Unexplained Infertility. American journal of reproductive immunology. 2015;73(6):557-67.

8. Bruno V, Svensson-Arvelund J, Rubér M, Berg G, Piccione E, Jenmalm MC, et al. Effects of low molecular weight heparin on the polarization and cytokine profile of macrophages and T helper cells in vitro. Scientific reports. 2018;8(1):1-9.

9. Dakhly DM, Bayoumi YA, Sharkawy M, Allah SHG, Hassan MA, Gouda HM, et al. Intralipid supplementation in women with recurrent spontaneous abortion and elevated levels of natural killer cells. International Journal of Gynecology & Obstetrics. 2016;135(3):324-7.

10. Lédée N, Vasseur C, Petitbarat M, Chevrier L, Vezmar K, Dray G, et al. Intralipid® may represent a new hope for patients with reproductive failures and simultaneously an over-immune endometrial activation. Journal of reproductive immunology. 2018;130:18-22.

11. Martini AE, Jasulaitis S, Fogg LF, Uhler ML, Hirshfeld-Cytron JE. Evaluating the utility of intralipid infusion to improve live birth rates in patients with recurrent pregnancy loss or recurrent implantation failure. Journal of human reproductive sciences. 2018;11(3):261.

12. Kang X, Wang T, He L, Xu H, Liu Z, Zhao A. Effect of low-dose aspirin on midluteal phase uterine artery blood flow in patients with recurrent pregnancy loss. Journal of Ultrasound in Medicine. 2016;35(12):2583-7.

13. Shaaban OM, Abbas AM, Zahran KM, Fathalla MM, Anan MA, Salman SA. Low-molecular-weight heparin for the treatment of unexplained recurrent

miscarriage with negative antiphospholipid antibodies: a randomized controlled trial. Clinical and Applied Thrombosis/Hemostasis. 2017;23(6):567-72.

14. Meng L, Lin J, Chen L, Wang Z, Liu M, Liu Y, et al. Effectiveness and potential mechanisms of intralipid in treating unexplained recurrent spontaneous abortion. Archives of gynecology and obstetrics. 2016;294(1):29-39.

15. Mekinian A, Cohen J, Alijotas-Reig J, Carbillon L, Nicaise-Roland P, Kayem G, et al. Unexplained recurrent miscarriage and recurrent implantation failure: is there a place for immunomodulation? American Journal of Reproductive Immunology. 2016;76(1):8-28.

16. Coulam CB, Acacio B. Does immunotherapy for treatment of reproductive failure enhance live births? American Journal of Reproductive Immunology. 2012;67(4):296-304.

17. Achilli C, Duran-Retamal M, Saab W, Serhal P, Seshadri S. The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and sterility. 2018;110(6):1089-100.

18. Singh N, Davis AA, Kumar S, Kriplani A. The effect of administration of intravenous intralipid on pregnancy outcomes in women with implantation failure after IVF/ICSI with non-donor oocytes: A randomised controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019;240:45-51.

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±SD	27.39 ± 4.55	27.40 ± 4.37	26.77 ± 4.26	
BMI(kg/m^2)				
Min.-Max.	22.0-30.6	21.5-29.7	23.5-29.9	0.246
Mean± SD	25.76 ± 2.66	25.44 ± 2.15	26.43 ± 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± S.D	11.16±0.65	11.16±0.68	11.19±0.58	
PT (S)				
Min.-Max.	9-12	9.0-11.0	9.00-10.0	0.416
Mean± S.D	11.64±0.74	11.588±0.67	11.53±0.68	
PTT (S)				
Min.-Max.	25.00-32.00	23.00-35.00	25.00-35.00	0.204
Mean± S.D	28.14±2.12	29.10±3.19	29.90±3.59	
TSH				
Min.-Max.	0.40-4.00	0.70-3.70	0.40-4.00	0.314
Mean± S.D	2.36±1.21	2.22±0.86	2.07±0.96	
Prolactin level				
Min.-Max.	3-18	5-18	5-22	0.059
Mean± S.D	12.45±3.75	13.65±3.62	11.57±3.50	
Postprandial Blood Sugar				
Min.-Max.	80-135	76-135	99-134	0.757
Mean± S.D	109.24±13.38	110.43±16.49	108.77±7.99	
Protein C				
Min.-Max.	80-134	100-140	70-140	0.436
Mean± S.D	115.55±13.91	118.03±9.87	111.23±17.29	
Protein S				
Min.-Max.	60-150	68-148	70-133	0.407
Mean± S.D	115.67±18.26	117.60±14.50	110.70±17.93	

Homocysteine				
Min.-Max.	5-10	5-9	5-9	0.402
Mean± S.D	7.00±1.46	6.93±1.44	7.37±1.35	
Anti cardiolipin:IgG				
Min.-Max.	5-8	5-8	5-8	0.400
Mean± S.D	6.27±1.07	6.47±1.14	6.63±0.96	
Anti cardiolipin:IgM				
Min.-Max.	3-5	3-5	3-5	0.258
Mean± S.D	4.15±0.76	4.00±0.74	3.83±0.79	

PT, prothrombine time, PTT, partial thromboplastin time, TSH, thyroid stimulating hormone, anticardiolipin IgG and IgM. Data are presented as mean ± 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 14th 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 placibo.