

Study of the Effect of Intralipid Infusion during Pregnancy as an Additive Treatment for Reducing Pregnancy Complications Caused by Antiphospholipid Antibody Syndrome

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Abstract

Aim: To evaluate the safety and efficacy of intralipid infusion in addition to other lines of treatment in reduction of complications caused by antiphospholipid antibody syndrome. **Methods:** This study was held in the period from June 1, 2016, to December 1, 2019. This study was conducted in the Department of Obstetrics and Gynecology, Tanta University on patients attending the antenatal care clinic and also on patients attending the researcher's private clinics for antenatal care, 105 patients were enrolled after application of strict inclusion and exclusion criteria. They were randomized into 2 groups. In group A (study group 1) the patients received in addition to the conventional basic treatment of APS, intralipid 20% (Frezenius, Clayton, NC, USA) in a dose of 4 ml diluted in 250 ml 0.9% regular saline IV and to be repeated every 2 weeks. In group B (control group 2) the patients received the conventional basic treatment of APS. The outcome measures were the incidence of pregnancy complications of APS namely fetal loss, premature delivery, IUGR and preeclampsia. **Results:** 49 patients were enrolled in the study group, and 48 patients were enrolled in the control group, after exclusion of the skipped cases. The demographic data and the gestational age at the beginning of the study show insignificant differences. There were insignificant differences as regard the gestational age at which the pregnancy was terminated and fetal birth weight in patients with positive ACL test, positive LA test and positive B2 however the mean gestational age at which pregnancy was terminated was higher in study group. Also, there was insignificant difference as regards no of patients who complicated with abortion or who completed to full term. But had significant decrease number of case who complicated with preeclampsia (8, 21 patients in study and control group respectively). **Con-**

Conclusion: Intralipid infusion is a promising treatment option for control and prevention of problems caused by antiphospholipid antibody syndrome.

Keywords

Antiphospholipid Antibody, Intralipid, Recurrent Pregnancy Loss

1. Introduction

The origin of antiphospholipid syndrome (APS) begins with the recognition of Wasserman's antibody, which was used to detect the presence of *Treponema pallidum* and found to bind the phospholipid cardiolipin [1]. After that the antibody was found in non syphilitic patients, indicating low specificity of this test and so a new term, biologic false positive serologic test for syphilis (BFP-STS), originates. In the 1950s, the BFP-STS was associated with another factor that causes inhibition of coagulation termed the lupus anticoagulant (LA) [2]. LA was discovered to be associated with thrombosis and pregnancy loss. In the 1990s, it was settled that antiphospholipid antibodies (APL) bind first to the circulating plasma protein b2-glycoprotein I (b2GPI) before binding to phospholipid.

Thrombus formation is the most important vascular pathology of APS, although the occurrence of this pathology at utero-placental vascular bed, but cannot simply explain the obstetric complications of the syndrome [3]. The *in vitro* studies revealed that APL produces a pro-coagulant state and thrombosis at the placental level through several postulated mechanisms, which had been disconfirmed by later studies, and also by histopathological examination of the placentas taken from APS women complicated by miscarriage [4]. Even Some researchers have postulated that obstetric APS is an inflammatory disorder [5], but even with these postulations, the evidence of inflammation isn't found in all laboratory animals or in all immunohistological analysis of placentae from APS patients [4].

1.1. Obstetric Complications

- Fetal and Recurrent Pregnancy Loss

It has been proven that APS is associated with recurrent embryonic or fetal loss, mostly in the fetal period (greater than 10 weeks of gestation) [6]. Observational studies have documented higher proportion of positive test for APL in women with recurrent pregnancy loss than in controls [7]. And also most studies report that 5% - 20% of women with recurrent pregnancy loss had positive test for APL [8].

- Preeclampsia

Preeclampsia is associated with APS (11% - 17%) [9]. with stronger association in women with early onset preeclampsia (<34 weeks of gestation) [10].

- Intrauterine Growth Restriction

15% - 30% of pregnancies in women with APS suffered from intrauterine growth restriction (IUGR) [11].

- Prematurity

Premature delivery is the commonest complication of APS in pregnancy (20% - 25% of patients; range 11% - 66%) as proved by many studies [12], and the most common cause of these premature deliveries is iatrogenic for management of complications of APS mainly pre-eclampsia and IUGR. Spontaneous premature delivery is less frequent [13].

How should antiphospholipid syndrome be managed during pregnancy and the postpartum period?

To improve maternal and neonatal outcome, APL treatment should be taken seriously. Low dose aspirin (LDA) and anticoagulation therapy with Low molecular weight heparin (LMWH) or fractionated heparin (FH) is the main line of treatment in pregnant patients with APS. In if patients are without history of thrombotic event LMWH should be taken at prophylactic dose and thrombo-prophylaxis should extend for 7 - 10 days after delivery, whoever if patient is with history of thrombotic events, LMWH should be taken at therapeutic doses and thrombo-prophylaxis should extend for 6 weeks after delivery. Oral anti-coagulants must be avoided before 6th week of gestation because of its confirmed teratogenic effect [14]. For women with uncontrollable obstetrical APS, observational case series suggested several alternatives: hydroxychloroquine (HCQ) [15], prednisone 10 mg/day till the end of 1st trimester [16], pravastatin 20 mg/day in cases of severe placental insufficiency with pre-eclampsia as soon as the complication is detected [17], and intravenous immunoglobulins (2 g/kg per month) and/or plasma exchange [18].

Intralipid is a fat emulsion containing egg phospholipids, soybean oil, and glycerin. It could be used for parenteral nutrition. Parenteral fat emulsions could accumulate in macrophages and lead to its malfunction. Despite the uncertainty of the immune mechanism by which intralipid act, but its active component, soybean oil inhibits type 1 T helper cells as a part of the pro-inflammatory mediators. There are many trials to use intralipid in obstetric fields including IVF, recurrent pregnancy loss and antiphospholipid antibody syndrome [19].

1.2. Aim

The aim of this paper is to evaluate the safety and efficacy of intralipid infusion in addition to other lines of treatment in reduction of complications caused by antiphospholipid antibody syndrome.

2. Subjects and Methods

This study was held in the period from June 1, 2016, to December 1, 2019. This study was conducted in the Department of Obstetrics and Gynecology, Tanta University on patients attending the antenatal care clinic and also on patients attending the researcher's private clinics for antenatal care. The number of pa-

tients enrolled in the study was 105 patients after application of inclusion and exclusion criteria.

All women were thoroughly informed about the study aims and through discussion about the procedure, associated benefits and risks and assigned written consent.

2.1. Inclusion Criteria

Pregnant women at booking date in the very 1st antenatal visit who were already diagnosed to have antiphospholipid syndrome (APS) by having repeatedly positive (two occasions at least) anticardiolipin antibodies ACL, lupus anticoagulant LAC or anti- β 2 glycoprotein-I antibody (anti- β 2GPI) with history of repeated (≥ 2) pregnancy loss (abortion, IUFD or premature delivery with failure of neonatal survival) due to APS.

2.2. Exclusion Criteria

Patients with gestational age ≥ 9 weeks calculated from 1st day of last menstrual period (LMP) and confirmed by measuring crown rump length (CRL), patients with diagnosed other auto-immune disorder, patients with chronic hypertension, diabetes mellitus, thyroid disorders, and patient with renal diseases were excluded. Also patients who requested to withdraw from the study at any point were excluded.

2.3. Baseline Evaluation

All the patients underwent full history taking, full examination, obstetric ultrasound scan and laboratory tests including CBC, urine analysis, glucose tolerance test, blood urea and serum creatinine, Rubella IgG and hepatitis B surface antigen (HBsAg).

The 105 patients included in the study were randomized in 2 groups according to sequence of computer-generated block-random numbers.

In group A (study group 1) (53 patients) the patients received in addition to the conventional basic treatment of APS (Dual low dose aspirin (LDA) (Ezcard 75 mg) once daily and Low molecular weight heparin (LMWH) (clexane 4000 IU) injection once daily, received in addition intralipid 20% (Frezenius, Clayton, NC, USA) in a dose of 4 ml diluted in 250 ml 0.9% regular saline to be infused IV and to be repeated every 2 weeks all over the pregnancy.

In group B (control group 2) (52 patients) the patients received the conventional basic treatment of APS (Dual low dose aspirin (LDA) (Ezcard 75mg) once daily and Low molecular weight heparin (LMWH) (clexane 4000 IU) injection once daily.

All the patients included in the study were subjected to meticulous antenatal care evaluation visits every two weeks then weekly after the 32nd week of gestation.

The outcome measures were the incidence of pregnancy complications of APS

namely fetal loss, premature delivery, IUGR and preeclampsia.

All statistics were performed using Minitab Ver.17 (Minitab Inc., USA).

3. Results

This study enrolled 105 patients who were assessed for eligibility after selection according to inclusion and exclusion criteria for eligibility. At the end of the study 49 patients were enrolled at study group, and 48 patients were enrolled at control group, after exclusion of the skipped cases. The demographic data and the gestational age at the beginning of the study of enrolled patients were demonstrated in **Table 1** with no significant differences between both groups.

Number of patients who were found to have positive ACL test in study and control group were 18 and 23 patients respectively, and there was insignificant differences between both groups as regard the gestational age at which the pregnancy was terminated in both groups (**Table 1**), however the mean gestational age at which pregnancy was terminated was higher in study group (32, 28.4 weeks in study and control group respectively). Also there was insignificant difference between both groups as regard fetal birth weight in patients with positive ACL test.

Table 1. Shows demographic data, gestational age and fetal birth weight for both groups.

	Group I (study group) N = 49			Group II (control group) N = 48			Chi-square	
	N	Range	Mean \pm S.D	N	Range	Mean \pm S.D	T value	P value
Age	49	22 - 41	30.96 \pm 5.57	48	22 - 41	31.56 \pm 5.96	0.52	0.608
BMI	49	17 - 38	27.53 \pm 6.65	48	18 - 40	29.79 \pm 6.93	-1.64	0.104
Gravidity	49	2 - 5	2.918 \pm 0.886	48	2 - 5	3.042 \pm 0.824	-0.71	0.48
Gestational age at inclusion	49	5 - 9	7.04 \pm 1.34	48	5 - 9	6.71 \pm 1.49	1.16	0.25
Gestational age ACL + ve at end of study	18	12 - 40	32.00 \pm 9.67	23	10 - 41	28.4 \pm 10.4	1.15	0.258
Gestational age LA + ve at end of study	29	10 - 40	31.86 \pm 9.14	21	11 - 41	31.2 \pm 10.1	0.24	0.81
Gestational age B2 + ve at end of study	6	18 - 40	34.33 \pm 8.21	9	12 - 39	33.22 \pm 8.64	0.25	0.806
Fetal weight at birth ACL + ve	14	900 - 3500	2357 \pm 752	17	900 - 3900	2276 \pm 949	0.26	0.794
Fetal weight at birth LA + ve	24	850 - 3850	2417 \pm 966	16	900 - 3750	2534 \pm 848	0.41	0.687
Fetal weight at birth B2 + ve	5	2000 - 3400	2740 \pm 572	8	800 - 3600	2300 \pm 787	1.16	0.271

Number of patients who were found to have positive LA test in study and control group were 29 and 21 patients respectively, and there was insignificant differences between both groups as regard the gestational age at which the pregnancy was terminated in both groups (**Table 1**), Also there was insignificant difference between both group as regard fetal birth weight in patients with positive LA test.

Number of patients who were found to have positive B2 test in study and control group were 6 and 9 patients respectively, and there was insignificant differences between both groups as regard the gestational age at which the pregnancy was terminated in both groups (**Table 1**), however the mean gestational age at which pregnancy was terminated was slight higher in study group (34.33, 33.22 weeks in study and control group respectively). Also there was insignificant difference between both groups as regard fetal birth weight in patients with positive B2 test.

There was insignificant difference between both groups as regards no of patients who were complicated with abortion (7 patients in study group, 11 patients in control group), preterm labor (18 patients in study group and 17 patients in control group). Also, insignificant difference between both groups as regards no of cases that completed full term pregnancy (24 patients in study group, and 20 patients in control group) (**Table 2**).

There was significant difference between both groups as regard number of cases who complicated with preeclampsia (8, 21 patients in study and control group respectively) with P value 0.003, but as regard the severity of developed preeclampsia there was insignificant difference between both groups (2 and 8 cases in study and control group respectively) (**Table 2**).

4. Discussion

Antiphospholipid antibody syndrome is considered one of the most important obstetric problems, and carry a high risk of early and late pregnancy loss, with other serious obstetrics complications like preeclampsia, early control of the condition is the keystone for prevention of complication, decrease its rate and even reduction of severity.

Table 2. Compares between number of complicated cases in both groups.

	Group I		Group II		Chi-square	P value
	yes	no	yes	no		
Abortion	7	42	11	37	0.692	0.405
Preterm labour	18	31	17	31	0.0058	0.939
Full term	24	25	20	28	0.269	0.604
preeclampsia	8	41	21	27	8.7	*0.003
Mild preeclampsia	6	43	13	35	3.38	0.065
Sever preeclampsia	2	47	8	40	4.15	0.041

In this study, 53 patients were randomly allocated in group a (study group) and received intralipid 20% (Frezenius, Clayton, NC, USA) in a dose of 4 ml diluted in 250 ml 0.9% regular saline repeated every 2 weeks all over the pregnancy in addition to the conventional basic treatment of APS. And 52 patients were randomly enrolled in group B (control group) and received the conventional basic treatment of APS.

After statistical analysis of the study, it was found that there was insignificant difference between both groups as regard gestational age at which termination of pregnancy was indicated, fetal birth weight, cases complicated by abortion or preterm labor, cases completed to full term pregnancy, but there was significant decrease in the number of cases who developed preeclampsia in study group, so intralipid may reduce preeclampsia as a complication for antiphospholipid syndrome yet not affect severity of preeclampsia.

Despite the insignificant difference between both group, but the mean gestational age at which pregnancy was terminated was noticeably higher in study group if compared with control group, number of case which was complicated with abortion was lower in study group, there was significant difference between both groups as regard number of cases who complicated with preeclampsia but as regard the severity of developed preeclampsia there was insignificant difference between both groups, the number of cases which complicated by preterm labor was higher in study group by only one case, and this may be attributed to decreased number of abortion in study group.

The idea of use intralipid in treatment of recurrent pregnancy loss based on practical study done by David A. Clark (1994) who had a double blind randomized controlled trial for evaluation of intralipid in control of recurrent spontaneous abortion on mice. And they found that intralipid was highly effective in preventing abortion in mice, and protection was prolonged [19].

Our study agrees with Dina M. R. Dakhly *et al.* (2016) who evaluated the efficacy of intralipid supplementation in women with recurrent spontaneous abortion over 296 women, the dose of intralipid was 2 mL diluted at 20% in 250 mL saline (half the dose used in our study) and they found that intralipid supplementation did not increase frequency of chemical pregnancy in cases who underwent IVF cycle, but despite intralipid infusion insignificantly increase live birth in cases with recurrent pregnancy loss, but they recommend for further studies of evaluation of intralipid infusion [20].

Our study agrees with Anne E. Martini *et al.* (2018) who retrospectively evaluated role of intralipid infusion in improving live birth rates And its cost-effective In patients with recurrent pregnancy loss and they found that there is no significant improvement in live birth rates with increase cost which reaches to be 681\$ per live birth, and they concluded that there is minimal benefits from intralipid infusion [21].

Léo P. *et al.* (2020) had studied the efficacy and safety of intralipid therapy to obtain live birth in women suffering from unexplained recurrent implantation failure and miscarriage, women enrolled in the study were from three French

university hospitals. They found that there were no significant differences between women who had successful pregnancies under intralipid with those with fetal loss, whoever also they concluded that intralipid could be an effective and safe therapy in women with unexplained recurrent miscarriages [22].

Our study agreed with Chiara A. *et al.* (2018) who had a Meta analysis study over the role of immunotherapy including intralipid in IVF and in the management of recurrent pregnancy loss. The literature search was performed using MEDLINE, PUBMED, CINAHL, and EMBASE until May 2017. They included randomized controlled trials only. They found that the available results showed controversy about the role of immunotherapy when used for improving reproductive outcomes including improving the live birth rate in women undergoing IVF treatment and in the prevention of idiopathic recurrent pregnancy loss. So they recommended use of immunotherapy in the context of research only [23].

Małgorzata J. *et al.* (2016) studied role of addition of intralipid to sildenafil and enoxaparin to improve pregnancy outcome in cases who suffered from 4 recurrent pregnancy losses (RPL) and IVF failures. And they found that this Combination therapy may generate successful IVF outcome, but need further study regarding safety. Our study was found on cases suffered from APS and the results were comparable to their study [24].

Carolyn B *et al.* (2012) studied the role of immunotherapy in treatment of reproductive failure either associated with antiphospholipid antibody syndrome or elevated NK cell activity to increase live birth. Treatment with intravenous immunoglobulin (IV Ig) (N = 242) and intralipid (N = 200) were compared. Heparin and aspirin were found to be successful in the treatment of women with APA with recurrent miscarriage but not with recurrent implantation failure. Intravenous immunoglobulin and intralipid had been successful in the treatment of recurrent miscarriage and recurrent implantation failure among women with elevated APA and/or NK cell activity. our study goes with that study in the importance of intravenous intralipid for control APS, but the insignificant results which was found in our study (significant in their study) may be attributed to larger number of patients and higher dose of intralipid given to the patients [25].

Jawharah *et al.* (2018) evaluated the efficacy of intralipid in case of multiple implantation failure, over 30 women during IVF cycle, and they found that the use of intralipid 20% might decrease rate of implantation failure in those patients [26].

The most important limitation of this study is the large number of skipped cases, so it was so difficult to follow-up the cases, and leads to decrease number of studied patients. histopathological examination of the placenta in both groups of patients which may give an idea about the effect of intralipid in histopathological level is another limitation.

5. Conclusion

Intralipid infusion is a promising treatment option for control and prevention of problems caused by antiphospholipid antibody syndrome, it significantly de-

crease number of cases complicated with preeclampsia, and also had a non-significant increased number of cases who reached full term pregnancy, so we advise further studies with larger number of patients and increasing dose of intralipid infusion used.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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