



ORIGINAL ARTICLE

## Live birth rates in patients of antiphospholipid syndrome treated with antiplatelet drugs as compared to antiplatelet drugs plus antithrombotic drugs.

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**ABSTRACT... Objective:** To compare antiplatelet drugs as compared to antiplatelet drugs plus antithrombotic drugs in patients of antiphospholipid syndrome. **Study Design:** Randomized Control Trial. **Setting:** Bahawal Victoria Hospital Bahawalpur. **Period:** October 2018 to October 2019. **Material & Methods:** Two hundred ten were included in the study. 105 patients were treated with loprin and 105 patients were treated with loprin and low molecular weight heparin (clexane). Pregnancy outcome were studied in both groups in terms of live fetal birth. **Results:** The mean age in group-A was 26.24. In group-B the mean age of patients was 26.50 years. 145 patients delivered full term babies while 65 patients delivered premature babies or presented with abortion. 63 patients in group-A and 82 patients in group-B delivered full term babies while 42 patients in group-A and 23 patients in group-B presented with abortion or delivered premature babies with significant p values of 0.005. **Conclusion:** Use of loprin and clexane 40 mg subcutaneously daily in patient with recurrent pregnancy loss due to antiphospholipid syndrome resulted in high live birth rates compared to patients who took only loprin.

**Key words:** Antiphospholipid Syndrome, Antiplatelet Drugs, Antithrombotic Drugs, Loprin.

### INTRODUCTION

An autoimmune condition is characterized by unusual response of one's own immune system to body. Antiphospholipid syndrome (APS) of pregnancy is also an autoimmune condition marked by appearance of attributable auto antibodies that endanger the pregnancy with various complications. It can cause recurrent miscarriages, intrauterine growth restriction (IUGR), intrauterine fetal demise, various complications relating to hypertension in pregnancy including severe preeclampsia with varying degrees of arterial and/or venous thrombosis. Incidence of APS auto antibodies is 1%–5% in general population, with dramatic increase of 15% in females with history of recurrent miscarriages, and 40% in females having systemic lupus erythematosus (SLE).<sup>1</sup>

Women diagnosed with obstetrical Anti phospholipid Syndrome have enhanced

probability of developing placental abruption, HELLP syndrome and arterial or venous thromboembolism that may lead to catastrophic antiphospholipid syndrome (CAPS).<sup>2</sup>

There are more chances of unsuccessful pregnancy in women with previous history of arterial or venous thrombosis or appearance of lupus anticoagulant. These women should be managed using multidisciplinary team approach. Combined care by a physician, anaesthetist and the obstetrician, is recommended for these females labelling them as a high-risk pregnancy. Care of these women starts in pre conceptional period with pre pregnancy counselling to identify and risk factors and contraindications, and to make consensus on treatment plan before pregnancy and during ante natal period.<sup>3</sup>

APS can present as a sole entity or can be present in conjunction with other autoimmune

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conditions like systemic Lupus Erythematosus or rheumatoid arthritis etc. labelling these as primary or secondary APS, respectively, at earlier times. But now these are preferably referred as APS with or without rheumatoid arthritis. Antiphospholipid (aPL) antibodies are related to APS clinically, but their role in disease pathogenesis or as epiphenomena is not yet understood, as aPL antibodies can be detected in up to 5% healthy persons.<sup>4</sup>

Pathogenesis of APS involves modification in haemostatic mechanisms of blood coagulation, however, process of thrombus formation is not fully understood until now. Among various hypothesis, one is defective cellular apoptotic mechanism, exposing phospholipids in cell membrane to wandering plasma proteins, like beta-2 glycoprotein-I. After binding, phospholipid-protein complex uncovers a neoepitope, the subsequent target of autoantibodies. The oxidized beta-2 glycoprotein-I bind and lead to activation of dendritic cells in a fashion similar to triggering by Toll-like receptor 4 (TLR-4), with potential of accelerating autoantibodies generation as shown by neoteric evidences.<sup>4</sup>

Laboratory manifestations of Antiphospholipid syndrome are characterized by presence of anticardiolipin [aCL] and anti-phosphatidylserine antibodies directed against membrane anionic phospholipids or the plasma proteins, primarily beta-2 glycoprotein I (apolipoprotein H) or is evidenced by presence of a circulating anticoagulant.<sup>5</sup>

Mainstay of treatment are Heparin and low-dose aspirin. History of patient is indicator for administration of therapeutic or prophylactic doses of heparin. To reduce the risk of thrombosis in mother, therapeutic window of anticoagulation therapy should be as small as possible during intrapartum period and this coverage should continue in postpartum period as well, as mother is at continuous risk of thromboembolism, HELLP syndrome and catastrophic antiphospholipid syndrome. Our suggestion is of 4 weekly clinical and biological surveillance, with frequency increasing towards term. The persistence of end

diastolic notch in uterine artery Doppler and serial ultrasound evaluation of fetal wellbeing appear to be the best predictor for placental vascular complications. Prognosis of pregnancy is increased with multidisciplinary team care along with optimum treatment resulting in successful outcome mostly.<sup>6</sup>

Pregnancy with APS is a high-risk pregnancy, requiring multi-disciplinary team approach including maternal and fetal medicine expert, rheumatologic, and haematological expertise. Close follow-up and vigilant foetal surveillance with serial obstetrical ultrasound Doppler assessment is required in case of any detected placental insufficiency.<sup>7</sup>

In patients with APS, heparin treatment is not very much practiced generally. So a study was done in Bahawal Victoria Hospital, comparing fetal outcome in term of live fetal births in clinically diagnosed antiphospholipid syndrome patients treated with low dose aspirin versus combination of low dose aspirin plus Heparin.

### Diagnostic Criteria

Antiphospholipid Syndrome is diagnosed using Sapporo's criteria. Designed and published in 1999, it includes Clinical and serological parameters.<sup>8</sup> With passage of time and collection of new evidences, a revised criterion called the Sydney's criteria was published in 2006.<sup>9</sup> This rationalized criterion requires one clinical and one laboratory feature to make diagnosis of antiphospholipid syndrome.

### Clinical Diagnosis

Patients with antiphospholipid syndrome present with a diverse array of symptoms, challenging the clinicians to diagnose underlying disease. The typical manifestations are fatal vascular thromboembolism, with poor obstetrical complications related to placental insufficiencies including recurrent miscarriages, intrauterine foetal demise and severe preeclampsia. However, no organ is spared from disease and lungs, heart, skin, brain, kidneys, eyes, adrenal glands, and liver, all can be affected by disease process.<sup>10</sup>

## Laboratory Diagnosis

The Sydney's criteria include significant modifications in laboratory parameters, including detection of LACs, aCL antibodies, or anti-2GPI antibodies. The inclusion of anti-2GPI antibodies in Sydney's criteria to make definitive diagnosis of APS is a significant change. Detection of antibodies, with sub classification of patients by number and type of antibodies is recommended. Stratification includes more than 1 laboratory criteria in any combination including sole presence of LACs, aCL antibodies or anti-2GPI antibodies present alone. In addition, isotype of aCL and anti-2GPI antibodies (ideally IgG antibodies) is also proposed to identify high risk patients.<sup>11</sup>

## MATERIAL & METHODS

This Randomized Controlled trial study was conducted at the department of obstetrics and gynecology, Bahawal Victoria Hospital Bahawalpur was conducted from October, 2018 to Oct, 2019, after approval from ethical committee (503/DME/QAMC).

Total 210 patients were included in the study. 105 patients were prescribed low dose aspirin (Ioprin) and rest 105 received combination of low dose aspirin (Ioprin) along with low molecular weight heparin (Clexane). The groups were formed on random allocation.

### Inclusion Criteria

1. Age 16 years or above.
2. Patients diagnosed clinically of antiphospholipid syndrome.

### Exclusion Criteria

Females having other causes of abortions or preterm labour like diabetes mellitus, hypertension, chromosomal abnormalities, uterine cervical shortening, intrauterine infection and local pathology.

Every female of antiphospholipid syndrome attending obs & Gynaecology OPD of Bahawalpur Victoria Hospital was included. The females selected for study were explained the potential risks involved and they joined only at their free

will. A written and informed consent was taken prior to inclusion in study process. The detail of study was conveyed to the patients and their queries was satisfactorily answered.

All included patients were placed in two groups named A and B by lottery method.

Patients included in "A" group were treated with Ioprin alone as soon as pregnancy was confirmed by fetal cardiac activity or gestational sac on ultrasound. Ioprin was given in dosage of 75 mg once daily and it was continued till the start of 34<sup>th</sup> week of pregnancy.

Patients in "B" group were treated with Ioprin along with either un-fractional heparin or Clexane as soon as pregnancy was confirmed by fetal cardiac activity or gestational sac on ultrasound. Clexane was given 40 mg once daily and was given subcutaneously. Uterine artery Doppler was done at 24<sup>th</sup> week of pregnancy. If it was found normal (uterine artery notch absent), Clexane was stopped and if it was found abnormal (uterine artery notch was present), Clexane was continued till the start of labor.

Patients were called at 4 weekly intervals in outdoor to see the final outcome in term of full-term live babies (delivery at or after 37 weeks of gestations). A proforma was used to collect the pertinent information from every patient.

### Fetal Outcome

Fetal outcome was measured in term of full-term live births (birth of a baby at or after 37 weeks gestation).

Data was analysed by using SPSS version 17.0. Mean and standard deviations were calculated for quantitative variables like age and weight (Kg) of patients. Frequency and percentages were calculated for qualitative variables like fetal outcome in term of live births in each group. Tables and graphs were used to present data.

## RESULTS

Two hundred sixteen (216) females fulfilled the inclusion criteria. 6 patients didn't give consent and were excluded. The mean age in group-A was

26.24 years. The mean of age was 26.50 years in participants of B group as shown in Table-I.

The mean weight was 54.19 Kg in participants of group A. It was 54 kg for participants of B group. 145 patients delivered full term babies while 65 patients delivered premature babies or presented with abortion as shown in Figure-1:

63 participants of A group and 82 participants of B group delivered full term babies while 42 A group participants and 23 participants of B group presented with abortion or delivered premature babies with significant p values of 0.005 as shown in Table-II.

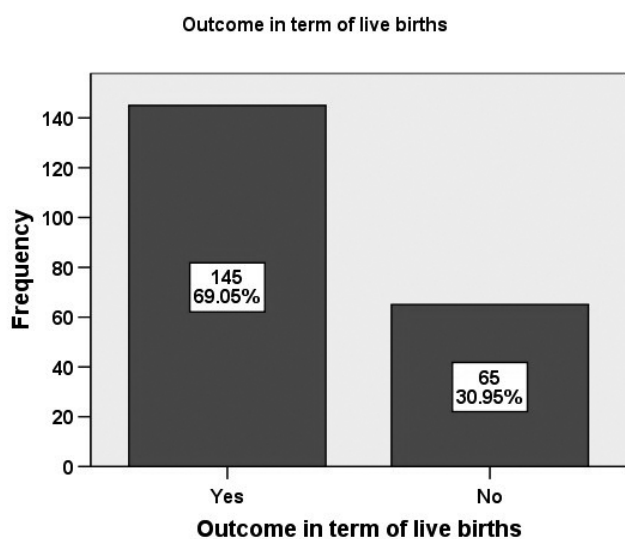


Figure-1. Frequency of outcome in term of live births.

## DISCUSSION

Recurrent pregnancy loss is a significant delimita of child bearing age females with incidence of about 1–2%. It is a prominent feature of antiphospholipid syndrome.<sup>12</sup> It has a wider spectrum of disease presentation ranging from asymptomatic to fatal APS catastroph. It is divided into primary and secondary APS, on basis of detection of aPL antibodies solely with idiopathic vascular thrombosis or association with other autoimmune problems i.e.SLE and rheumatoid arthritis, respectively.<sup>13</sup>

Among the various causes of recurrent miscarriages, APS is the most predominant and treatable reason. The causes of early pregnancy loss are poorly understood with different mechanisms proposed, which include defective differentiation, invasion and migration of trophoblastic cells with some complement mediated inflammatory reactions in decidua. Late fetal losses are explained by thrombi in bed of placenta.<sup>14</sup>

In our study among 210 participants of study, 69.05% had successful outcome. 60% in group-A (treated with Loprin) and 78.1% in group-B (treated with Loprin plus Clexane) achieved live birth. These results were comparable to other studies. Brenner et al<sup>15</sup> conducted the study which included patients with APS as well as those with hereditary thrombophilia's i.e. Factor V Leiden mutations, protein C and S deficiency. used

Age Group of Patients	Group of Patients		Total	P=Value
	Group-a (loprin)	Group-b (loprin + heparin)		
16-24 years of age	38 (47.5%)	42 (52.5%)	80 (100%)	0.819
25-32 years of age	42 (52.5%)	38 (47.5%)	80 (100%)	
33-40 years of age	25 (50%)	25 (50%)	50 (100%)	
total	105 (50%)	105 (50%)	210 (100%)	

Table-I. Patients in age group.

Group of Patients	Outcome in Term of Live Births		Total	P=Value
	Yes	No		
Group-A (loprin)	63 (60%)	42 (40%)	105 (100%)	0.005
Group-B (loprin plus heparin)	82 (78.1%)	23 (21.9%)	105 (100%)	
Total	145 (69%)	65 (31%)	210 (100%)	

Table-II. Outcome in term of live births in different groups of patients.

aspirin 75 mg daily and They used Inj. Enoxaparin 40 subcutaneously once daily to those having solitary thrombophilias and 80 mg S/C OD to those having combined defects. Aspirin in dose of 75 mg was prescribed additionally to woman having antiphospholipid syndrome. Successful outcome in terms of live births was as high as 86%.

Study conducted at University of Sheffield, England, had all the participants with serological evidence of APS. Enoxaparin in 20 mg subcutaneously dose was administered with Loprin achieving live birth rate of 80%. 5% females reported for preterm delivery but there was no evidence of perinatal mortality.<sup>16</sup>

Supporting our supposition that earlier administration of low molecular weight Heparin reduces the incidence of early pregnancy losses, Ismail et al. studied the effects of administering LMWH to females having recurrent miscarriages and Antiphospholipid syndrome, in preconceptional period. They administered 80mg enoxaparin S/C per day with aspirin after documented evidence of ovulation. This regimen resulted in marked reduction of early pregnancy losses. However, if fertilization does not occur then this preconceptional LMWH proves to have many disadvantages. So our recommendation is to use clexane after confirmation of pregnancy to avoid undesirable adverse effect.<sup>17</sup>

There was no remarkable difference in complications towards end of pregnancy related to antiphospholipid antibodies i.e.in intra uterine growth restriction, IUFD, pre-eclampsia placental abruption or preterm delivery before 34 weeks postulated to be due to administration of low dose aspirin in participants of both groups, with proved to prevent IUGR and preeclampsia in Antiphospholipid syndrome patients.<sup>18</sup>

Malinowski A et al<sup>19</sup> concluded the benefit of prescribing combination of low-dose of acetylsalicylic acid and LMWH for increasing the positive outcome of pregnancy as compared to both regimens prescribed alone. Sole administration of low-dose of acetylsalicylic acid

resulted in successful outcome rate of 89.3%, while the success rates in low molecular weight heparin alone group equated 81.1%. Group who received the combination resulted in 92.5% pregnancy success rates.

Boda Z et al.<sup>20</sup> found that only 2 among 22 pregnancies, without any thromboprophylaxis during pregnancy had successful outcome (9.1%). Contrary to this, 8 out 9 pregnant females who received combination high dose LMWH and low dose aspirin gave birth to healthy new-borns (88.8%).

Dendinos S et al.<sup>21</sup> studied the comparison in terms of live births among females who received combination of Low molecular weight heparin plus low dose aspirin versus those who received low dose aspirin alone. Live births were 29/40 (72.5%) and 15/38 (39.5%), respectively, among two groups with P=0.003.

During study of Kutteh WH<sup>22</sup>, 11 of 25 (44%) females who were administered low dose aspirin had successful outcome in term of healthy neonates, whereas 20 out of 25 (80%) females who received LMWH and aspirin in combination had viable neonates ( $p < 0.05$ ). However no considerable differences were observed among two groups in terms of period of gestation at time of delivery ( $37.8 \pm 2.1$  vs  $37.2 \pm 3.4$  weeks), mode of delivery i.e. caesarean sections (18% vs 20%), or other complications.

In native study done by Fawad S<sup>23</sup> inference in term of live births, period of gestation at birth and pregnancy complications etc. patients who were given low dose aspirin and clexane 40 mg subcutaneously once per day starting from 6-8 weeks to 35 and 37 weeks respectively. 93% females had live birth with 75% delivered at full term but 18% gave birth to preterm babies. 7% women lost their pregnancy in earlier gestation loss. There was one early neonatal death the reason behind which was extreme prematurity. Haemorrhage related complication were not observed in any of the selected study population. Literature proves the safety and efficacy of low dose aspirin LMWH in pregnancy.<sup>24</sup>

The variation in inferences of our study from that of literature, are may be, due to selection of study population with some patients strongly fulfilling the clinical criteria but were not having strongly positive serological parameters. (Probable APS). Our participants gained high live birth but preterm delivery rate was also high.

## CONCLUSION

Use of low dose aspirin and low molecular weight heparin (Enoxaprin) 40 mg subcutaneously daily in females with recurrent miscarriages due to antiphospholipid syndrome achieved high live birth rates in contrast to females who received loprin alone. In view of these results, combination of low-molecular-weight heparin (clexane) and low dose loprin prophylaxis is suggested for pregnant ladies with antiphospholipid syndrome, continued for whole pregnancy.




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2	Khiaynat Sarwar Hashmi	Writing article, Review, Results complication.	
3	Rabia Qasim	Data collection.	
4	Noreena Saba	References, Data collection.	