

# Outcome of Prophylactic Therapy with LMWH and Aspirin in Pregnancy with Antiphospholipid Syndrome

Farah Hameed, Samia Shuja

## Abstract:

**Objective:** To determine the fetal outcome after prophylactic therapy with low molecular weight heparin and aspirin in pregnant woman with recurrent pregnancy loss (antiphospholipid syndrome)

**Study Design and Setting:** This is retrospective observational study conducted in Department of obstetrics and gynecology at Indus hospital Karachi from 20 December 2016 to 30 September 2022.

**Methodology;** The study group include 39 pregnant woman with antiphospholipid syndrome (recurrent pregnancy loss) presented at Sheikh Saeed campus of Indus Hospital Karachi from 2016 to 2022. Patients were diagnosed with APS on the basis of Sapporo clinical criteria for APS. All these patients were treated with prophylactic therapy with aspirin and low molecular weight heparin throughout pregnancy. The primary outcome was live birth. Statistical analysis was done through SPSS version 26.

**Result:** Prophylactic therapy with low molecular weight heparin and aspirin in pregnant woman with recurrent pregnancy loss has a significant impact on the fetal outcome. 79.5% delivered alive babies. 12.8 % experienced miscarriage. 2.6 % had termination of pregnancy due to congenital malformation. 5.2% were unable to follow-up.

**Conclusion;** Prophylactic therapy with low molecular weight heparin and aspirin has significantly improved live birth rate (79.5%) in patients with recurrent pregnancy loss with antiphospholipid syndrome.

**Keyword;** Antiphospholipid syndrome (APS), Aspirin, Low Molecular Weight Heparin (LMWH)

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## INTRODUCTION

Antiphospholipid syndrome is a significant and manageable contributor to repeated pregnancy loss. The incidence of antiphospholipid syndrome is 20-40% in women with recurrent miscarriage.<sup>1</sup> Among healthy women without history of recurrent miscarriage, antiphospholipid antibodies are detected between 1-5%. These antibodies are found upto 15% in women with recurrent pregnancy loss. Among general population, prevalence of antiphospholipid syndrome is 0.5%.<sup>2</sup> The incidence of recurrent miscarriage is 1%. Recurrent miscarriage can be caused by chromosomal, anatomic, hormonal (progesterone, estrogens, diabetes or thyroid disease), coagulation or rly pregnancy, platelet abnormalities. About 10-15% of such women, the cause of recurrent pregnancy loss is antiphospholipid syndrome.

Antiphospholipid antibodies can be detected upto 5-20% in women recurrent pregnancy loss.<sup>3</sup> When a woman with APS (antiphospholipid syndrome) conceive, the incidence of spontaneous abortion is quite high. Without treatment about 90% of pregnancies end up in miscarriage.<sup>4</sup> APS has a strong impact on pregnancy, It not only affects early pregnancy but late pregnancy as well, In early pregnancy it is associated with recurrent miscarriage. APS is associated with preterm delivery, pre-eclampsia, intrauterine growth restriction and intrauterine fetal death. These complication are mainly due to effect of antiphospholipid antibodies on trophoblast differentiation and invasion leading to placental infarctions, and thrombosis.<sup>5,6</sup> The Sapporo/Sydney Criteria for diagnosis of definite APS is based on clinical as well as laboratory findings.<sup>7</sup>

1-Vascular thrombosis: One or more episodes of arterial or venous thrombosis, or thrombosis of small vessels in any organ or tissue, confirmed through Doppler. It should exclude vasculitis.

2-Pregnancy outcomes: a) One or more deaths of a morphologically normal fetus after the 10th week of gestation, confirmed by ultrasound or autopsy. b) One or more premature births of a morphologically normal fetus before the 34th week of gestation, due to eclampsia,

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pre-eclampsia, or placental insufficiency. c) Three or more spontaneous abortions before the 10th week of gestation, with maternal hormonal or anatomical abnormalities, and paternal and maternal chromosomal causes excluded.

**Laboratory Criteria:** (a) Presence of lupus anticoagulant antibody (LA) in the plasma on two or more occasions, at least 12 weeks apart, detected according to the International Society on Thrombosis and Hemostasis (ISTH) guidelines.

(b) Moderate (> 40) to high (> 80) titers of IgG or IgM anticardiolipin antibodies (ACL) on two or more occasions, at least 12 weeks apart, detected via standard ELISA test.

c) Presence of IgG or IgM anti-beta 2-GPI antibodies in the plasma on two or more occasions, at least 12 weeks apart, detected by standard ELISA test

The key pathological process driving APS-associated pregnancy complications is thrombus formation in placenta that leads to compromised placental functions and impaired fetomaternal exchange. The disrupted exchange between mother and fetus ultimately contributes to development of obstetric complications. The presence of placental infarcts as observed in histological studies by DE Wolf further corroborates this understanding of the underlying disease process.<sup>8</sup> Thrombus formation is a complication associated with suboptimal placentation, leading to restricted fetal growth and development. Studies conducted by Yamada et al have demonstrated a link between antiphospholipid antibodies and compromised pregnancy outcomes specifically low birth weight and preterm labour.<sup>9</sup> Plozin et al have also observed a correlation between antiphospholipid antibodies and fetal growth restrictions.<sup>10</sup> Compromised circulation between the fetus and placenta is a risk factor for late pregnancy complication, such as placental abruption, which can have devastating consequence including fetal death and still birth.<sup>11</sup>

The standard treatment regimen for antiphospholipid syndrome in pregnancy typically centers around heparin administration. Heparin possesses a distinct property that enable it to bind to antiphospholipid antibodies and inhibiting their interaction with trophoblastic tissues. This leads to improved blood flow, reduced risk of placental thrombosis and infarction, and ultimately, fewer complication in late pregnancy. Aspirin exerts a beneficial thromboprophylactic effect by suppressing platelet aggregation thereby reducing risk of thrombotic event.<sup>12</sup>

#### METHODOLOGY:

This is retrospective observational study. After obtaining approval from the ethical review board of the institution IRB number IHHN -2022-019, data was collected. All pregnant woman with recurrent pregnancy loss (antiphospholipid syndrome) presented at Sheikh Saeed campus of Indus Hospital Karachi from 20 Dec2016 to 30

September 2022. As this was retrospective study so informed consent was not required, Patients were diagnosed with aPLS only on the basis of Sapporo /Sydney clinical criteria for aPLS. No laboratory testing for antiphospholipid syndrome was done as these were already pregnant. All these patients were treated with aspirin and low molecular weight heparin. The time of initiation of treatment was between 7 to 17weeks. All patients were treated with daily Aspirin 75mg and low molecular weight heparin 1mg/kg body weight. Compliance was ensured by recollection of empty ampules. All patients were regularly followed through serial scans and plan was made to deliver at 37 weeks if both mother and fetus doing well. LMWH and Aspirin was stopped one day before elective delivery. The primary outcome was live birth. Total 39 pregnant women meeting inclusion criteria were undergoing prophylactic therapy. Statistical analysis was done through SPSS version 26. Inclusion criteria: All pregnant woman with recurrent pregnancy loss with aPLS only on the basis of Sapporo /Sydney clinical criteria for aPLS. Exclusion criteria: recurrent pregnancy loss due to uterine anomalies, Cervical incompetence, cardiovascular, renal disease, previous history of thromboembolic diseases, BMI >30kg/m<sup>2</sup>, Pregnancy loss due to known genetic and hormonal factors, any pre-existing medical disorder that has an impact on pregnancy outcome, Uterine fibroid which might cause complications during pregnancy

As this is retrospective observational study so randomized and controlled groups are not required. As all women with APS were treated with daily Aspirin 75mg and low molecular weight heparin 1mg/kg bodyweight so there was no control and randomized group.

#### RESULTS:

The median interquartile range (IQR) of start time of their therapy 11 weeks (7-17). Their mean age 29.9±5.6 year. BMI 27.2± 3.8, delivery time was 37(36-37) weeks, still births 2(1-3) and Number of miscarriages was 5(3-4). Moreover, for current pregnancy 25.6% women develop GDM, 5.1% develop Pregnancy Induced Hypertension (PIH) while only 1(2.6%) had hypothyroidism. If talk Regarding fetal outcome, 79.5%(31)women delivered alive babies 79.5%(31) and 12.8 (5%)had miscarriage. One woman was diagnosed with anencephaly(2.6%) so termination of pregnancy done as per patient wish. and two(5.2%) patients were lost for follow up.. Furthermore, out of 31 alive babies 17(54.8%) were females. Besides that, all babies had a healthy weight. The median (IQR) of male and female weight was 2.8kg (2.4-2.9) and 2.7 kg(2.1-3.0) kg (Table 1). Additionally, no significant difference was observed between fetal outcome and other comorbidity of patients like gestational diabetes mellitus, pregnancy induced hypertension and BMI

**DISCUSSION:**

Our study, treatment was initiated between 7-17weeks of pregnancy. Our study found that live birth rate with combine treatment LMWH and aspirin is 79.5 % which is quite high. Almost all patient were delivered at 37weeks.All babies have normal birth weight. The miscarriage rate is 12.8 % after using the therapy which is significantly lower. Around 5% of the women developed pregnancy induced

hypertension. So, the combined treatment is not only associated with improved live birth rate but also associated with reduced incidence of miscarriage, pregnancy induced hypertension, pre-eclampsia and fetal growth restriction and preterm delivery.

By decreasing the trophoblastic apoptosis and increasing generation of proteases essential for trophoblastic-endometrial interaction, Heparin supports a healthy implantation process. In vitro studies have shown that low molecular weight heparin influences angiogenesis in placental villi and modulates vascular endothelial growth factor (VEGF) dysregulation. Additionally heparin has been found to inhibit complement activation potentially reducing risk of pregnancy complication,

A key point of discussion is the optimal timing for commencing treatment, specifically whether we should begin before pregnancy or be delayed until after conception. Research by Laklouk et al demonstrated enhanced live birth following administration of Heparin and Aspirin. They compared two groups: one that received therapy 2-3months prior to conception and another that received therapy after pregnancy confirmation. The study found no significant difference in miscarriage and live birth rates between two groups, suggesting that the timing of treatment initiation did not have a substantial impact.<sup>13</sup>

Hamulyak et al conducted a meta-analysis between two groups with recurrent pregnancy loss and antiphospholipid syndrome.<sup>14</sup>Combination treatment with LMWH and Aspirin was associated with increase live birth rate. Yu also conducted a metanalysis on treatment of recurrent miscarriage (associated with APS).Yu found reduced incidence of miscarriage, pre-eclampsia and fetal growth restriction. Furthermore, treatment is associated with markedly improved gestational age at birth and increased live birth rate.<sup>15</sup> These results are very similar to our study.

Juneja et al has also reported significant improved live birth rate after treatment with Aspirin and LMWH<sup>16</sup>.Rekha et al found that Asprin alone is associated with 82% live birth while combination of Aspirin and LMWH is associated with

Table:1 Study participants age .BMI and time of start of therapy and Time of delivery

<b>Age Years</b>	
Mean ±SD	29.9±5.6
<b>BMI</b>	
Mean ±SD	27.2±3.8
<b>Thrombolytic therapy start time (Weeks)</b> n (%)	
Median(IQR)	11(7-17)
<b>Delivery time (Weeks)</b> n(%)	
Median (IQR)	37(36-37)

Table 2: Current pregnancy and morbidity

DM	3(7.7)
GDM	10(25.6%)
PIH	2(5.1%)
HTN/ Chronic HTN	3(7.7)
Hypothyroidism	1(2.6)
<b>Fetal Outcome</b> n(%)	
Alive	31(79.5)
Miscarriage	5(12.8)
Lost to followup	2(5.2)
Termination	1(2.6)
<b>Gender of Baby</b> n(%)	
Male	14(45.2)
Female	17(54.8)
<b>Weight of male (kg)</b> n(%)	
Median(IQR)	2.8(2.4-2.9)
<b>Weight of female (kg) Median(IQR)</b>	
	2.7(2.1-3.0)

Table 3: Association between Fetal outcome and other characteristics of participants

	Fetal Outcome					p-value
	Alive n%	Misscairrage n%	Lost to followup n%	Termination n%	Total n%	
<b>Age years</b>						
≤29.9	16(51.6)	3(60)	2(100)	1(100)	22(56.4)	0.734 <sup>?</sup>
>29	15(48.4)	2(40)	-	-	17(43.6)	
<b>DM</b>	3(9.7)	-	-	-	3(7.9)	0.721 <sup>?</sup>
<b>GDM</b>	9(29)	1(20)	-	-	10(26.3)	0.721 <sup>?</sup>
<b>PIH</b>	2(6.5)	-	-	-	2(5.3)	
<b>HTN</b>	3(9.7)	-	-	-	3(7.9)	

92.5% live birth which is quite satisfactory.<sup>17</sup>

The use of low molecular weight Heparin in conjunction with Aspirin is widely viewed as

a safe and effective treatment approach. Studies have shown that LMWH can exert a

favorable influence on trophoblastic implantation and apoptosis, suggesting a potential role in promoting healthy placental function. The optimal timing for heparin administration to promote implantation success may coincide with the time of implantation itself, aligning with the standard administration schedule for LMWH. LMWHs are given subcutaneously once a day. The subcutaneous delivery of heparin provide considerable benefits compared to unfractionated heparin such as enhanced bioavailability, longer plasma half-life and more reliable pharmacokinetics and pharmacodynamic profiles, as well as reduced potential for osteoporosis. LMWH is also not associated with thrombocytopenia. The antithrombotic effect of LMWH is to inhibit factor Xa more effectively than factor IIa. Furthermore, LMWH does not cross the placenta and is safe for the fetus.

Aspirin is being used to mitigate the risk of miscarriage and improve pregnancy outcome in women with history of recurrent miscarriage. The main role of aspirin to maintain a balance between thromboxane A2 and prostacyclin, Thromboxane A1 has platelet aggregation and vasoconstriction properties while prostacyclin promotes vasodilatation. Low dose aspirin administration daily shifts balance in favour of prostacyclin leading to vasodilatation and improved blood flow. Manisha et al conducted a study on two groups with recurrent miscarriage. One group received only Aspirin while second group received combination therapy (Aspirin and LMWH). The combination group had a significantly lower number of miscarriages 32% vs. 54%,  $P < 0.001$  and a significantly higher number of live births 69% vs 41%. There were no significant differences in the number of preterm deliveries (<37 weeks) between the two groups.<sup>18</sup> Katarina Jeremiae et al reported pre-eclampsia occurs 15% despite treatment with low dose aspirin and LMWH.<sup>19</sup> While in our study 5% of the women developed PIH (pregnancy induced hypertension). In a study by David MO it was found that in pregnant women (with previous history of miscarriage) after treatment of low dose enoxaparin with low dose aspirin 80% live births and 20% miscarriage.<sup>20</sup> It is almost similar to our study with 79.5% live birth and miscarriage rate is 12.8.

Beta 2-glycoprotein I (b2GPI), a phospholipid binding protein, is a key antigenic target in APS. This protein is expressed on multiple cell types associated with coagulation and placental development. The binding of aPL to beta 2-glycoprotein I (b2GPI) on trophoblast, decidual and endometrial cells, endothelial cells play a critical role in pathogenesis of APS. The presence of aPLs has been found

to disrupt trophoblast function, inhibiting differentiation and invasiveness while inducing cellular injury and apoptosis which can compromise placental development and pregnancy outcome. These antibodies also promote pro-inflammatory phenotype in stromal cells. Additionally, aPLs have been found to inhibit angiogenesis in endometrial endothelial cells. Tanimura et al conducted prospective observational study to see effect of low-dose aspirin (LDA) and unfractionated heparin (UFH) in women with recurrent pregnancy loss with anti-beta2glycoprotein I/HLA-DR autoantibodies. The live birth rate in the LDA/UFH group was 87.2% than that in the non-LDA/non-UFH group 50.0%. This is very significant difference. Furthermore, women with RPL, the pregnancy complication rate in the LDA/UFH group was significantly lower than that in the non-LDA/non-UFH group (5.9% vs 50%).<sup>21</sup>

When a woman present with recurrent pregnancy loss, the most important step is to test for antiphospholipid antibodies. These antibodies are also underlying cause for rheumatic diseases so patients are referred to rheumatologist to identify early signs of rheumatic diseases, Antiphospholipid syndrome is characterized by thrombus formation in arterial and venous circulation. This thrombus formation is associated with pregnancy morbidity. As per Sydney criteria, obstetric APS is early onset of severe preeclampsia before 34 weeks. This clinical criteria emphasize diagnosed clinically on basis of obstetric history, this also includes three consecutive miscarriages before 12 weeks or explained fetal death after 12 weeks pregnancy provided that there should be no history of thrombus

Although the connection between APS and pregnancy complications is well established, a 2013 consensus report on 14th International Congress on Antiphospholipid Antibodies noted that many studies investigating the association between APS and miscarriage fail to meet the strict laboratory criteria outlined in the Sydney criteria, making link between RPL and aPL questionable.<sup>22</sup>

The European league against rheumatoid arthritis and American college of rheumatology (EULAR/ACR) has introduced new criteria for APS in 2023. It includes clinical and laboratory criteria. This criteria has high specificity. The clinical criteria includes thrombotic event, pregnancy morbidity and neurological and cardiac manifestation. The thrombus should be at uncommon sites. The new criteria for pregnancy morbidity has also been changed regarding pregnancy duration and timing of preeclampsia. The criteria has extended clinical spectrum of APS by including microvascular and cardiac valve diseases. Furthermore, the laboratory domains includes lupus anticoagulant, anticardiolipin and beta2 glycoprotein I antibodies. The most important change is the titer of these antibodies. The titer should be medium or high. The new criteria does not include low titer. For EULAR/ACR 2023 a score of three or more than three, both clinical as well as laboratory criteria is

required to establish diagnosis of APS.<sup>23</sup>

Mercier et al conducted a comparative study to assess prevalence of APS on basis of Sydney and EULAR criteria, the prevalence was 14% with Sydney criteria and only 1.3% with EULAR criteria. The most important aspect of this study is no significant difference in previous pregnancy outcome was found. The high specificity of EULAR/ACR is associated with significant loss of number of cases of APS.<sup>22</sup> So we can treat patients with OAPS (obstetric antiphospholipid syndrome) diagnosed on the basis of clinical Sydney criteria and we can improve live birth rate in such patients with recurrent pregnancy loss.

Limitation; Our limitation was small sample size.

### CONCLUSION:

The combined treatment with LMWH and aspirin in women with antiphospholipid syndrome is associated with significant improvement in fetal outcome.

**Conflicts of Interest:** Nil

**Source of Funding:** Nil

**Acknowledgement:** Nil

### Authors Contribution:

**Farah Hameed:** Identified, literature research and prepared the manuscript and take full responsibility for its clinical integrity

**Samia Shuja:** Final review of manuscript

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