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Perinatal outcomes in indian women with Antiphospholipid Antibody Syndrome (APS): Five year experience from a tertiary care centre

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ABSTRACT

Background: Antiphospholipid Syndrome (APS) is a systemic autoimmune thrombophilic condition characterized by obstetric manifestations, including pregnancy loss, preeclampsia and fetal growth restriction. Early diagnosis and management are key to improve maternal and neonatal outcomes.
Objective: The aim of this study is to assess the perinatal outcomes in APS, the development of various adverse pregnancy outcomes (APO), and their association with specific antibody profiles.
Material methods: This observational study was carried out on booked cases of singleton pregnancy and diagnosed cases of primary APS in our High-Risk Pregnancy (HRP) clinic from January 2018 to December 2022 after approval from institutional ethics committee. Forty-three confirmed cases of primary APS were enrolled and started on low-dose aspirin and low-molecular-weight heparin (LMWH) as per the patient's body weight after confirmation of fetal heart activity radiologically until 36 weeks of gestation as a standard of care.
Results: Forty patients (93 %) had obstetric APS, and three patients (7 %) had thrombotic APS. During the course of the current pregnancy, adverse pregnancy outcomes (APO) developed in 12 (30 %) out of 40 cases of obstetric APS and in all 3 patients with thrombotic APS. Preeclampsia was seen in 11 (25.5 %), FGR in 12 (27.9 %), and preterm birth in 7 (16.2 %) cases. Patients with an antibody profile showing the presence of Anti-β2 GP-I positivity and ACL positivity had fewer APOs (20 % and 29 %) in comparison to patients with a LA and triple positive antibody profile (55 % and 50 %).
Conclusion: Treatment of pregnant women with APS causes significant improvement in the live birth rate. The late pregnancy complications like preeclampsia, FGR, and premature birth, occurring despite treatment still remains a challenge and emphasizes the need for stringent antepartum surveillance and timely delivery.

Introduction

Antiphospholipid Syndrome (APS) is a systemic autoimmune thrombophilic condition characterized by the occurrence of arterial or venous thrombotic events and/ or pregnancy morbidity in the presence of the circulating antiphospholipid antibody (aPL) in the blood that recognize and attack phospholipid-binding proteins [1,2]. The main types of aPL of concern are lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-beta-2-glycoprotein antibodies (aB2GP1) [3]. Patients are allocated to classification categories on the basis of positivity to more than one test (category I) or to a single test (category II) [4]. APS is a rare disease with a prevalence of 0.05 %. It is 3.5 times more common in women as compared to men [5,6].

Pregnancy is a hypercoagulable state. In pregnant women with APS, hyper coagulability, along with an elevated level of coagulated factors in the blood, an increased activated protein C resistance, an increased concentration of plasminogen activator inhibitors, and decreased protein S levels, might lead to life-threatening complications and adverse pregnancy outcomes like preeclampsia, pregnancy loss, thromboembolism, preterm delivery, and increased perinatal mortality [6]. Without medical management, about 25 % of patients diagnosed with APS can give birth to a healthy neonate. With the introduction of low-dose aspirin (LDA) and low-molecular-weight heparin (LMWH) therapy as standard of care, successful perinatal outcomes have greatly improved to about 70 % [6–10].

Material and methods

In this study, we aimed to assess the perinatal outcomes in APS, the development of various adverse pregnancy outcomes (APO) and their

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association with specific antibody profiles. This observational study was carried out on booked cases of singleton pregnancy and diagnosed cases of primary APS in our High-Risk Pregnancy (HRP) clinic from January 2018 to December 2022 after approval from institutional ethics committee. The diagnosis of APS was made according to the revised international classification criteria given by Miyakis et al. in 2006 [3].

Patients were screened for history of unexplained death of a normal fetus after the 10th week of gestation, history of premature birth of a morphologically normal neonate before 34th week of gestation because of placental abruption, severe early onset preeclampsia, unexplained fetal growth restriction (FGR) in prior pregnancy, and history of three or more consecutive unexplained abortions. Focussed past and family history regarding any thrombotic events was taken. After ruling out other causes of recurrent abortions like chromosomal anomalies, uncontrolled diabetes, thyroid dysfunction, fetal structural anomalies and infections like syphilis, patients were enrolled in the study. After taking informed consent, the blood samples were tested for anti-phospholipid antibodies (APLA) twice (12 weeks apart). Anticardiolipin antibodies (aCL) were tested by enzyme-linked immunosorbent assay (ELISA) (AESKULISA cardiolipin, AESKU Diagnostics, Wendelsheim, Germany). Lupus anticoagulant (LA) was tested using kaolin clotting time (Sigma Diagnostics, St. Louis, MO, USA). Anti-β2 GP-I was tested by an enzyme immunoassay for the quantitative determination of IgG or IgM antibodies to β2 GP-I (GA Generic Assays GmbH, Dahlewitz/Berlin, Germany) as per standards. Secondary APS cases were excluded after doing reflex anti Ro/La and antinuclear antibody (ANA) testing.

Forty-three confirmed cases of primary APS were enrolled and started on low-dose aspirin (75 mg/day) and low-molecular-weight heparin (LMWH) (40 mg/60 mg s.c. daily as per the patient's body weight) after confirmation of fetal heart activity radiologically and continued until 36 weeks of gestation as a standard of care. LMWH was switched over to unfractionated heparin (UFH) (5000 IU s.c., twice daily) at 36 completed weeks and was stopped 12 h before labor induction or emergency cesarean section (CS) and 24 h in elective settings as per standard of care and started again 12 h after delivery and continued in postpartum for 6 weeks.

Results

Out of a total of 43 patients, 20 (46.5 %) were in the age range of 21 to 30 years, and the rest, 23 (53.4 %), were between 31 and 40 years. The majority of patients, 29 (67.4 %), were gravida 4 to 6, 13 (30.2 %) patients were gravida 1–3, and one (2.4 %) was gravida > 6 (Table 1).

The majority (90.7 %) of the patients with APS belonged to category II (single positive) (LA/aCL/anti-β2 GP-I), while the rest (9.3 %) belonged to category I (double/triple positive). Patients with antibody profile showing presence of Anti-β2 GP-I positivity and ACL positive had lesser APOs (20 % and 29 % respectively) in comparison to patients with LA and triple positive antibody profile (55 % and 50 %) (Table 2).

Forty patients (93 %) had obstetric APS and 3 patients (7 %) had thrombotic APS. Of the 3 patients with thrombotic APS, 2 had a history of venous thrombosis (DVT) and 1 had a history of arterial thrombosis (stroke) in a previous pregnancy. During the course of current pregnancy adverse pregnancy outcomes (APO) developed in 12 (30 %) out of 40 cases of obstetric APS and all 3 patients of thrombotic APS. Preeclampsia was seen in 11 (25.5 %), Fetal growth retardation (FGR) in 12 (27.9 %), and preterm birth (<37 weeks) in 7 (16.2 %) cases. Preeclampsia was most recurring APO in patients with LA positivity (Table 3).

Out of 43, 21 (48.8 %) women had spontaneous onset of labour, out of which 19 (90.5 %) were delivered vaginally and in 2 (9.5 %) caesarean section (CS) was done. In 12 (27.9 %) cases, artificial induction was done using oxytocin, dinoprostone gel alone, Foley's catheter and dinoprostone gel, out of which 9 (75 %) were delivered vaginally and in 3 (25 %) CS was done. In the rest of 10 (23.3 %) cases, elective CS was done.

The most common indication was previous CS (not willing or fit for trial of labor) in 5 (33.3 %) cases, fetal distress, seen in 3 (20 %) cases, malpresentation in 4 (26.6 %) cases, Absent end diastolic flow (AEDF) on ultrasonography, antepartum eclampsia, and second stage arrest in 1 (6.7 %) case each (Table 5).

In our study one patient with preeclampsia had intrapartum abruption. There was no case of thrombotic event in present pregnancy or postpartum. There was no stillbirth or neonatal death in this study. Two babies had neonatal intensive care unit stay.

For treatment, aspirin plus LMWH, followed by UFH, was given to all 43 patients. However, despite the treatment and strict monitoring, APO's like preeclampsia and FGR were seen.

Discussion

APS has been recognized as one of the important causes of recurrent abortions for a long time. It is the most common thrombotic disorder causing recurrent pregnancy loss. Perinatal complications during previous pregnancies are a usual indication for screening and evaluation of APS during pregnancy [11]. In a study by Oshiro et al., it was concluded that more than 80 % of cases with APLA had at least one fetal death, compared with less than 25 % in women with negative APLA status [12].

In our study, there was no fetal death in index pregnancy with treatment. This compares favourably with a study by Dadhwal et al., in

Table 1
Age and gravida status distribution of patients with and without adverse pregnancy outcomes.

Maternal age	Total patients (n = 43)	APO (adverse pregnancy outcomes)	no APO (no adverse pregnancy outcomes)
21 –30 years	20 (46.5 %)	07	13
31 –40 years	23 (53.5 %)	08	15
Gravida status	**Total patients (n = 43)**	**APO (adverse pregnancy outcomes)**	**no APO (no adverse pregnancy outcomes)**
1 –3	13 (30.2 %)	04	09
4 –6	29 (67.4 %)	11	18
> 6	01 (2.4 %)	01	-

Table 2
Antibody profile of APLA positive patients.

Category	APLA (Antiphospholipid antibody)	Total patients (n = 43)	APO (adverse pregnancy outcome)	no APO (no adverse pregnancy outcome)
II	B2GP +ive	23 (53.5 %)	06	17
	aCL +ive	07 (16.2 %)	02	05
	LA +ive	09 (20.9 %)	05	04
I	Double +ive	0		
	Triple +ive	04 (9.3 %)	02	02

Table 3
Adverse pregnancy outcome (APO) in APLA positive patients.

APO Adverse pregnancy outcomes (n = 43)		
Fetal loss	0	
Preeclampsia	11 (25.5 %)	05 LA +ive; 04 β2 GP-I +ive; 02 triple +ive
Preterm labour	07 (16.2 %)	01 LA +ive; 04 β2 GP-I +ive; 02 triple +ive
FGR	12 (27.9 %)	02 LA +ive; 08 β2 GP-I +ive; 01aCL +ive; 01 triple +ive
Neonatal death	0	

Table 4
Labour onset and Mode of delivery.

Labour onset	Total patients (n = 43)	Vaginal delivery	Caesarean section
Induced	12 (27.9 %)	09	03
Spontaneous	21 (48.8 %)	19	02

Table 5
Indication of cesarean section.

Indication	Total patients (n = 15)
Fetal distress	03
Malpresentation	04
Previous CS not willing/fit for trial of labour	05
Absent end diastolic flow (AEDF)	01
Antepartum eclampsia	01
2nd stage arrest	01

which a successful pregnancy outcome of an 85.7 % live birth rate was seen with treatment and 4.6 % in untreated pregnancies [13].

In our study, the majority (90.7 %) of the patients with APS were single positive (53.4 % anti-β2 GP-I +ive, 20.9 % LA +ive, and 16.2 % aCL +ive), while the rest (9.3 %) were triple positive. Similarly, in the study by Dhadhwal et al., 78.6 % were single positive (category II) and 21.4 % were double positive (category I) [13]. Whereas in a study by Ruffati et al., 66 % of patients had more than one positive antibody (category I) and 34 % were single positive (category II), which may be attributable to the differences in the population domains [4].

In this study, despite treatment, the adverse outcomes noted were FGR, preeclampsia, and preterm birth in 27.9 %, 25.5 %, and 16.2 % of cases, respectively. In a study by Bats et al. on 33 pregnancies with APS after treatment, there were 18.2 % cases of FGR, 24.2 % of preterm deliveries, and 3 % of preeclampsia [14]. Similarly, in a study by F. Nili et al., it was found that preeclampsia was seen in 24.1 % of cases and preterm birth in 46.6 % of cases of APS [15]. Dhadhwal et al. concluded that despite treatment, 7 % developed severe preeclampsia and 10 % had severe IUGR [13].

This study amalgamated the present evidence of successful pregnancy outcome following treatment in patients with APS, especially in the Indian scenario where the awareness of this clinical syndrome is still limited. The continued occurrence of late maternal and fetal complications like preeclampsia, FGR and premature birth despite treatment further questions the need for stringent antepartum surveillance and timely delivery. The role of newer treatment modalities like intravenous immunoglobulins and plasmapharesis needs to be defined by trials on these patients.

The strength of our study is that this presents the data from well-established high-risk clinic of a tertiary care institution of north India, as there are very few studies from India in this context. The limitations of the study are small sample size.

Conclusion

Treatment of pregnant women with APS causes a significant improvement in the live birth rate. APOs like FGR and preeclampsia occur despite treatment; strict monitoring and timely delivery are the keys to successful perinatal outcomes. Further large, prospective studies are needed, along with the evaluation of other non-criterion antibodies, which are the subject of investigation for their value in APS and especially for identifying seronegative antiphospholipid syndrome (SNAPS) patients with antibodies against phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI), vimentin/cardiolipin complex, annexin V, and annexin II.

The occurrence of late pregnancy complications despite treatment still remains a challenge and emphasizes the need for better antepartum surveillance and further exploration of new treatment modalities.

Ethical justification

The study was performed in line with the principles of declaration of Helsinki. Approval granted by Institutional Ethical Committee PGIMER, Chandigarh (Intramural) Ethical number - INT/IEC/2024/SPL-674, dated 05.06.2024, vide reference number: IEC-INT/2024/Study-1969.

CRediT authorship contribution statement

Mahak Bhardwaj: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Vanita Jain:** Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Minakshi Rohilla:** Validation, Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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