RESEARCH
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EVALUATING AND COMPARING THE OBSTETRIC OUTCOME IN ANTIPHOSPHOLIPID SYNDROME AND, SERO NEGATIVE ANTIPHOSPHOLIPID SYNDROME IN LOW SOCIO ECONOMIC GROUP.

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Abstract
Background: Antiphospholipid syndrome (APS) is an autoimmune disorder known to impact pregnancy outcomes, leading to complications such as recurrent miscarriage, thrombosis, and preeclampsia. Aim: This study aimed to comprehensively evaluate and compare obstetric outcomes in patients treated for APS, and seronegative APS (SN APS). Methods and Material: The study was conducted involving antenatal mothers with recurrent pregnancy loss or bad obstetric history. Patients were categorized into two groups: APS, and SN APS, based on specific diagnostic criteria. Each group received tailored treatment regimens according to their diagnosis. Patients were closely monitored throughout pregnancy, and obstetric outcomes were documented and analysed using statistical methods. Results: Among the observed complications, early pregnancy loss (EPL) was the most common adverse event. Preterm labour and preterm birth were frequent outcomes, Other complications included placental insufficiency and abruptio placenta. In terms of treatments, low-dose aspirin and LMW Heparin were commonly administered. The majority of preterm babies required neonatal intensive care unit (NICU) admission. Take home baby rate was 86%. Conclusion: This study highlights the significant obstetric challenges faced by patients with APS, and SN APS. The management of these conditions is complex, and timely treatment can lead to improved outcomes. Positive results in SN APS was in par with APS
Key-words: Antiphospholipid syndrome, Seronegative Antiphospholipid syndrome, miscarriage.

INTRODUCTION

In 1983 – 86, Dr. Graham Hughes and his team described the antiphospholipid syndrome and since then it is one of the most common autoimmune disorders [1]. In obstetrics, APS is now regarded as the most prothrombotic cause of recurrent pregnancy loss – with pregnancy success improving from below 20% to a current live birth rate of over 70% with treatment. This multisystem disorder is diagnosed by the presence of Lupus anti-coagulant (LAC) and anticardiolipin antibody (ACL) in associated with venous and or arterial thrombosis or pregnancy complications. APS may be classified at primary or secondary (when associated with SLE).

The diagnostic criteria for Antiphospholipid Syndrome (APS) were initially formulated in the late 1990s and revised in 2000. Modified criteria for APS include vascular thrombosis, pregnancy morbidity, and laboratory criteria. Diagnosis requires fulfillment of at least one clinical and one laboratory criterion. Specific obstetric criteria for APS encompass fetal growth retardation, intrauterine fetal death, placental insufficiency, among others, while non-specific criteria involve recurrent embryonic miscarriage. Additionally, there exists a subset of patients labeled as sero-negative APS, who exhibit APS features despite persistently negative antiphospholipid antibodies. Current diagnostic challenges in sero-negative APS prompt exploration of non-criteria tests, though their diagnostic value remains under scrutiny. Recent studies suggest that these tests may enhance diagnostic accuracy in APS. Notably, the 2019 EULAR recommendations advocate for combined therapy, including low-dose aspirin and prophylactic heparin, for pregnant women with a history of obstetric APS. The primary objective of ongoing research is to evaluate and compare obstetric outcomes among patients treated for APS and sero-negative APS, particularly within low socio-economic status groups.

METHODS AND MATERIAL:

Study design and setting: This was a Cohort study conducted in the Department of Obstetrics and Gynecology, Vinayaka mission's Kirupananda Variyar Medical College and Hospitals, Seeragapadi, Salem for a period of 1 year from august 2022 to September 2023.

Study participants:

Antenatal mothers with the recurrent pregnancy loss/ Bad obstetric history attending the Department of Obstetrics and Gynecology, Vinayaka mission's Kirupananda Variyar Medical College and Hospitals, Seeragapadi, Salem was taken as study population.

The inclusion criteria for this study comprise female patients aged 20 to 40 years who have a documented history of adverse obstetric events. Specifically, these events could include

recurrent miscarriages, fetal growth retardation, intrauterine fetal death, or other complications during pregnancy. Conversely, exclusion criteria involve patients with incomplete medical records or those presenting with comorbidities that might independently influence obstetric outcomes. Such comorbidities include infections, genetic disorders, and uterine malformations, which could confound the assessment of outcomes related to Antiphospholipid Syndrome (APS) or sero-negative APS. By establishing these criteria, the study aims to ensure a focused investigation into the obstetric outcomes of interest within the specified patient population.

Sampling method: Purposive sampling was done and all the patients fulfilling the inclusion and exclusion criteria during the study period was taken into the study

Data collection and analysis:

Patients underwent comprehensive assessments to diagnose antiphospholipid syndrome (APS). We have adopted the revised sappora / Sydney criteria for diagnosing APS and also considered the non criteria APS features as an independent criteria. The laboratory test (as per Sydney criteria) done were anticardiolipin (acl) IgG, IgM, anti ß2 Glyco protein (ß2GP1) IgG/IgM and lupus anticoagulant (LAC). ACL was performed by ELISA and interpretation of titre was 40 GPL as low, 40 – 80 GPL as moderate and > 80 as high.LAC was detected by activated partial thromboplastin time (aPTT) followed by dilute Russel's Viper Venom Test (dRVVT). Anti ß2 GP1 antibodies also detected by ELISA technique. Repetition of APS screening was not done as all our patients were from low Socio-economic status.

Subsequently, these patients were categorized into two distinct groups: APS, and Seronegative APS. Seronegative APS were not subjected to non criteria test due to financial restrictions. Each patient within these groups received Low-Dose Aspirin, and low molecular weight Heparin, and corticosteroids, in accordance with their specific diagnosis and medical needs.

Following the initiation of treatment, patients was diligently monitored throughout the course of their pregnancy until its conclusion. This ongoing observation aimed to assess and document the obstetric outcomes and complications experienced by each patient group, thereby contributing to a comprehensive understanding of how these autoimmune disorders impact pregnancy and childbirth. Data was analyzed with Statistical Package for Social Sciences (SPSS -IBM) software version 21. Descriptive analysis using frequency/percentages.

Ethical consideration:

The study was conducted only after obtaining institutional ethical committee approval. Prior to any participation in the study, informed consent was obtained from all eligible patients. The informed consent process included detailed explanations of the study's objectives, procedures, potential risks, and benefits. Patients had the opportunity to ask questions and was assured of their right to withdraw from the study at any point without affecting their medical care. The research team strictly adhered to patient confidentiality guidelines. All data collected was anonymized and stored securely to protect patient privacy. Any potential risks associated with participation, such as those related to medications or additional medical procedures, was carefully weighed against the potential benefits of improving the understanding and management of these conditions.

RESULTS:

This study encompassed fifteen patients aged between 22 and 37 years who presented at the Obstetrics Department OP of Vinayaga Medical Mission Hospital. These patients underwent evaluations for autoimmune disorders such as antiphospholipid syndrome (APS). Based on the test results, the patients were categorized into two distinct groups, as outlined in Table I.

Commonest disorders coexisting was GDM/DM and Hypothyroidism. Out of the 6 patients with DM/GDM, 1 and 5 were respectively in APS and SN APS. Similarly, out of the 6 patients with hypothyroidism, 2 and 4 were in APS and SN APS respectively.

Table 1: Profile of the study participants

Group	Number of patients	Frequency	Age range (Years)
APS	8	53.3%	24 – 37
SN APS	7	46.6%	28 – 36

Table 2: Lab investigations of the study participants

S No	Lab investigations +ve results	Frequency	Percentage
1	LAC (aPTT + DRVV)	8	53.3%
2	ACL (IgG, IgM)	4	26.6%
3	ß2 GP (IgG, IgM)	4	26.6%

Totally eight were positive for APS and the rest were negative for APS

All the four who tested positive for ACL and the four who were positive for ß2GP were LAC positive.

Table 3: Previous obstetric score/ event in different groups:

Obstetric event	APS		SN APS		Total
	N	%	N	%	
Early pregnancy loss	5	41.6	7	58.3	12
Termination of pregnancy	1	100	0	0	1
Fetal death	0	0	1	100	1
Live baby	3	50	3	50	6

Among the obstetric complications observed, early pregnancy loss (EPL) was the most adverse event, with 12 cases reported. One termination of pregnancy (TOP) occurred between 23 to 24 weeks of gestation, in the APS group. This termination was carried out due to severe intrauterine growth restriction (IUGR), abnormal Doppler findings, oligohydramnios, and imminent eclampsia. The histopathology of the placenta in two patients indicated abnormal placentation, characterized by obliterated villi, extensive infarction, thrombosis, necrosis, fibrin deposition, and a dysmature placenta. One patient belonged to the APS group and one to the SN APS group.

Table 4: Treatment given in different groups:

Treatment	APS		SN APS		Total
	N	%	N	%	
LDA Only	1	100 %	0	0	1
LDA + Heparin	6	46.1	7	53.8	13
LDA+Heparin+Steroid	1	100 %	0	0	1

One APS patient refused Heparin and she had Early pregnancy loss. Rest of the fourteen patients were started on LDA + LMW Heparin. One patient from APS group had thrombocytopenia and hence steroid was given.

Table 5: Complications in different groups:

Complications	APS		SN APS		Total
	N	%	N	%	
IUGR Placental Insufficiency	4	57.1	3	42.8	7
Abruptio Placenta	1	100	-	-	1

One of the specific clinical features of APS is placental insufficiency. 7 of our patients were under regular surveillance by serial USG for fetal growth, liquor and Doppler. One of our patients who had thrombocytopenia had abruptio placenta at around 30 weeks of gestation warranting emergency LSCS with Baby needing prolonged NICU care. There was no maternal nor fetal mortality.

On evaluating the obstetric outcome (Table 6) of these 15 pregnancies it was shown that while there was 14 EPL in untreated group, there was only one EPL in treated group that too she was the one who refused Heparin.

Table 6: Obstetric outcome in different groups

There was two termination of pregnancies in untreated groups. In the treated group there was one fetal death in SN APS due to uteroplacental insufficiency at 30 weeks. There were four preterm deliveries and all babies needed NICU care. (Two was PROM, one for growth < than 5th centile, and one for non-reassuring NST. There were 9 term deliveries. One baby was born with the birth weight range of 1.4 kg to 2 kg, and it was a preterm. Seven babies were of birth weight of 2.1 to 2.5 kg. Five babies was born with the birth wt. range 2.6 kg to 3kg. There was only one baby > 3 kg.

Term babies had normal newborn period. The four preterm babies needed NICU care. One was admitted for meconium aspiration. Rest was all for routine basic preterm care. Three preterm babies were from APS and one from SN APS. All babies got discharged without any mortality.

DISCUSSION:

The present research aimed to assess and compare the obstetric outcomes of patients treated for antiphospholipid syndrome, and seronegative antiphospholipid syndrome. A total of 15 patients were included in the study. Among them, eight tested negative for Lupus Anticoagulant (LAC) as determined by DRVVT/aPTT testing, four tested positive for anticardiolipin antibodies (ACL), and four tested positive for ß2 Glycoprotein antibodies. Autoimmune thrombocytopenia was observed in 40-50% of individuals with antiphospholipid syndrome,[7,8,9] and it is often challenging to distinguish it from idiopathic thrombocytopenic purpura. The treatment approach for both conditions is similar. In our study, one patient experienced thrombocytopenia, from the antiphospholipid antibody-positive group.

One of the most common and severe complications in antiphospholipid syndrome is thrombosis, which can occur in arterial or venous vessels. Approximately 65-70% of thrombotic events are venous in nature.[10,11] Upper limb thrombosis is less frequent than lower limb thrombosis. None of our patient had DVT. A large cohort study by Silver RM et al.[12] indicated that the incidence of thrombosis during pregnancy or the postpartum period in APS patients is 25%. Left lower limb thrombosis is the most common site, often attributed to the compression of the left common iliac vein by the gravid uterus.[13]

In our study, 6 out of 15 patients were diagnosed with hypothyroidism, with four in the seronegative antiphospholipid syndrome (SN APS) group and two in the antiphospholipid syndrome (APS) group, In our study, six patients had diabetes or gestational diabetes, with one in the APS group and five in the SN APS group.

The presence of antiphospholipid antibodies (APLA) was detected in 11-17% of patients with pre-eclampsia[14]. Yamada H et al.'s[15] prospective evaluation of over 1000 women with APLA revealed a significantly increased risk of pregnancy-induced hypertension (PIH) with an odds ratio of 5.5, and severe PIH with an odds ratio of 8.1.[16]. This suggests a strong association between APS and severe preterm PIH. None of our patients in the treated group had PIH.

Recurrent early miscarriage (REM) is a common obstetric complication in antiphospholipid syndrome. Andreoli L et al.[16] and the University of Utah group[17] reported that a low percentage (2-6% and <5%, respectively) of women with REM have positive APL. However, de Jesus GR et al.[18] found a higher incidence of 10-15% in women with recurrent fetal loss and a notably higher incidence of 50-20% was reported by Branch DW et al.[19]. A cohort study by Oshiro BT et al.[20] showed a pregnancy loss rate of 10% in the APLA-negative group, while it was 50% in the APLA-positive group during the fetal period. A prospective follow-up study by Erton ZB et al.[21], which included 55 APL-positive pregnant patients, observed that 27% of these pregnancies ended in early pregnancy loss. Among the remaining 40 pregnancies, APL-related composite morbidity was noted in 9 (23%) pregnancies, including six cases of preterm labour and delivery (PTLD) and three cases of fetal death.

The pathogenesis of placental insufficiency leading to inadequate uteroplacental circulation and subsequent fetal loss is attributed to thrombosis[22]. The Still Birth Collaborative Research Network[23] conducted a multicenter, population-based, case-control study of stillbirth and found that 10% of fetal deaths occurring after 20 weeks of gestation were positive for APL. Early delivery due to severe pre-eclampsia and/or placental insufficiency serves as a highly specific obstetric clinical criterion. A strong association between pre-eclampsia and APS is reported, with 11-17% of pre-eclampsia patients testing positive for APS, particularly in cases of severe preterm pre-eclampsia.[14] Yamada H et al.[15] also conducted a prospective evaluation of over 1000 women and found an increased risk of severe pregnancy-induced hypertension with an odds ratio of 8:1.

Limitations:

Our study does have a few limitations. We did not perform repeat APLA tests after 12 weeks, primarily because our patients come from a low socioeconomic background, making frequent testing financially challenging. Despite having ruled out other potential causes of recurrent early miscarriage (REM), we did not conduct a comprehensive panel of other antibodies due to cost constraints. In our approach to patients with seronegative antiphospholipid syndrome (SN APS), we adopted a more lenient stance and even in cases where APLA tests showed low positive results, which sometimes did not meet the criteria for inclusion or formal diagnosis.

Key message: This study emphasizes the varying obstetric outcomes in Antiphospholipid Syndrome (APS), and Seronegative APS patients, highlighting the need for comprehensive evaluation and tailored treatments to improve pregnancy results, even in cases where patients may not meet all diagnostic criteria.

CONCLUSION:

As rheumatologists work on revising the diagnostic criteria for antiphospholipid syndrome (APS), obstetricians are encountering a growing number of patients with seronegative APS (SN APS) who do not meet the established classification criteria. Unfortunately, due to financial constraints, we are often unable to conduct non-criteria tests, particularly in countries with limited resources like ours. However, it is crucial not to overlook or leave them untreated, as they may experience severe adverse obstetric events. Obstetricians strongly believe that it is imperative to develop more permissive treatment protocols for SN APS. Our experience with treating patients with APS and SN APS has been highly promising. We have followed the 2019 EULAR recommendations in managing SN APS patients, and the outcomes have been consistently positive.

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Conflicts of interest: There are no conflicts of interest.

Ethical statement:

Institutional ethical committee accepted this study. The study was approved by the institutional human ethics committee, Vinayaka mission's, Kirupananda Variyar medical college and hospitals, Salem, Tamilnadu. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

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Authors' contributions:

Dr Divya. M - conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing;

Dr Jeyamani B -conceptualization, methodology, writing—original draft, writing—review and editing, visualization, supervision, writing—original draft. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY:

All datasets generated or analysed during this study are included in the manuscript.

INFORMED CONSENT:

Written informed consent was obtained from the participants before enrolling in the study

References

1. *Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. British Medical Journal (Clinical research ed.). 1983 Oct 10;287(6399):1088.*
2. *Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. The Lancet. 2010 Oct 30;376(9751):1498-509.*
3. *Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, Amoura Z, Andrade D, Andreoli L, Artim-Esen B, Atsumi T. The 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Arthritis & Rheumatology. 2023 Oct;75(10):1687-702.*
4. *Tebo AE, Jaskowski TD, Phansalkar AR, Litwin CM, Branch DW, Hill HR. Diagnostic performance of phospholipid-specific assays for the evaluation of antiphospholipid syndrome. American journal of clinical pathology. 2008 Jun 1;129(6):870-5.*
5. *Liu X, Zhu L, Liu H, Cai Q, Yun Z, Sun F, Jia Y, Guo J, Li C. Non-criteria antiphospholipid antibodies in antiphospholipid syndrome: Diagnostic value added. Frontiers in Immunology. 2022 Oct 26;13:972012.*
6. *Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, Cuadrado MJ, Dörner T, Ferrer-Oliveras R, Hambly K, Khamashta MA. EULAR recommendations for the management of antiphospholipid syndrome in adults. Annals of the rheumatic diseases. 2019 Oct 1;78(10):1296-304.*
7. *Alarcón-Segovia D, Pérez-Vázquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. InSeminars in arthritis and rheumatism 1992 Apr 1 (Vol. 21, No. 5, pp. 275-286). WB Saunders.*
8. *ASHERSON RA, KHAMASHTA MA, Ordi-Ros JO, DERKSEN RH, MACHIN SJ, Barquinero JO, OUTT HH, Harris EN, VILARDELL-TORRES MI, HUGHES GR. The "primary" antiphospholipid syndrome: major clinical and serological features. Medicine. 1989 Nov 1;68(6):366-74.*
9. *Harris EN, Asherson RA, Gharavi AE, Morgan SH, Derue G, Hughes GR. Thrombocytopenia in SLE and related autoimmune disorders: association with anticardiolipin antibody. British journal of haematology. 1985 Feb;59(2):227-30.*
10. *Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. New England Journal of Medicine. 1995 Apr 13;332(15):993-7.*
11. *Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Annals of Internal Medicine. 1992 Aug 15;117(4):303-8.*
12. *SILVER RM, DRAPER ML, SCOTT JR, LYON JL, READING J, D WARE BR. Clinical consequences of antiphospholipid antibodies: an historic cohort study. Obstetrics & Gynecology. 1994 Mar 1;83(3):372-7.*
13. *Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M. Pulmonary embolism in pregnancy. The Lancet. 2010 Feb 6;375(9713):500-12.*

14.D WARE BR, ANDRES R, DIGRE KB, ROTE NS, SCOTT JR. The association of antiphospholipid antibodies with severe preeclampsia. Obstetrics & Gynecology. 1989 Apr 1;73(4):541-5.
15. Yamada H, Atsumi T, Kobashi G, Ota C, Kato EH, Tsuruga N, Ohta K, Yasuda S, Koike T, Minakami H. Antiphospholipid antibodies increase the risk of pregnancy-induced hypertension and adverse pregnancy outcomes. Journal of reproductive immunology. 2009 Jan 1;79(2):188-95.
16. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, de Jesus GR, Erkan D, APS ACTION. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. Arthritis care & research. 2013 Nov;65(11):1869-73.
17. Bowman ZS, Wünsche V, Porter TF, Silver RM, Branch DW. Prevalence of antiphospholipid antibodies and risk of subsequent adverse obstetric outcomes in women with prior pregnancy loss. Journal of Reproductive Immunology. 2015 Feb 1;107:59-63.
18. de Jesus GR, Agmon-Levin N, Andrade CA, Andreoli L, Chighizola CB, Porter TF, Salmon J, Silver RM, Tincani A, Branch DW. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. Autoimmunity reviews. 2014 Aug 1;13(8):795-813.
19. Branch DW, Silver RM, Porter TF. Obstetric antiphospholipid syndrome: current uncertainties should guide our way. Lupus. 2010 Apr;19(4):446-52.
20. Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW. Antiphospholipid antibodies and fetal death. Obstetrics & Gynecology. 1996 Apr 1;87(4):489-93.
21. Erton ZB, Sevim E, De Jesús GR, Cervera R, Ji L, Pengo V, Ugarte A, Andrade D, Andreoli L, Atsumi T, Fortin PR. Pregnancy outcomes in antiphospholipid antibody positive patients: prospective results from the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ('Registry'). Lupus Science & Medicine. 2022 Jun 1;9(1):e000633.
22. Giannakopoulos B, Passam F, Rahgozar S, Krilis SA. Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood. 2007 Jan 15;109(2):422-30.
23. Silver RM, Parker CB, Reddy UM, Goldenberg R, Coustan D, Dudley DJ, Saade GR, Stoll B, Koch MA, Conway D, Bukowski R. Antiphospholipid antibodies in stillbirth. Obstetrics and gynecology. 2013 Sep;122(3):641.