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To study the association of Antiphospholipid syndrome in patients with bad obstetric history

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Abstract
Background: Antiphospholipid antibodies (APLA) are the most important autoimmune cause of recurrent pregnancy loss (RPL). These pregnancies can be saved if diagnosed and treated adequately. This can be achieved by routine screening for APLA in pregnant women with a bad obstetric history (BOH) and unexplained fetal loss.
Aims and Objective: To study the association of antiphosholipid antibodies in women with BOH and thus evaluating the usefulness of routine screening of serum antiphosholipid antibodies in patients with unexplained fetal wastage and BOH for better outcome.
Material and method: The present study was a prospective study carried out in Department of Obstetrics and Gynaecology at SDM College of Medical Science and Hospital, Dharwad, India, over a period of 1 year from November 2015 to October 2016. Women with bad obstetric history meeting the inclusion and exclusion criteria were recruited in the study and underwent screening for APLA which included Lupus Anticoagulant (LA), Anticardiolipin (ACL) and Anti Beta 2 glycoprotein (β2-GP1) 1 IgG/ IgM. Those tested positive were retested 12 weeks later to confirm the result. Then the various adverse pregnancy outcomes were studied in both APLA positive and negative groups. The APLA positive cases were started with low dose aspirin and heparin.
Results: The study showed that 12 out of 57 cases of BOH were APLA positive. Among the positive APLA group, 2 samples were positive for ACL IgM, 8 samples were LA positive and 1 positive for Anti β2-GP1 IgG and IgM each. The maternal and fetal outcomes were analysed in the study. There was statistically significant difference in the obstetric outcome among the APLA positive patients started on heparin as compared to APLA negative patients.
Conclusion: It is a proved fact that APLA interferes with the normal development of the uteroplacental circulation to cause early and late pregnancy loss. Hence screening for APLA in patients with BOH will help in identifying the cause of recurrent fetal loss and its treatment will improve the obstetric outcome.

Keywords: Antiphospholipid syndrome, bad obstetric

Introduction
Bad obstetric history (BOH) implies previous unfavourable fetal outcome in terms of two or more consecutive spontaneous miscarriages, early neonatal deaths, stillbirths, intrauterine fetal deaths, intrauterine growth restriction and congenital anomalies. For any given pregnancy, the reported risk of pregnancy loss is 15% and the likelihood of consecutive three losses, would be 0.34% [1]. These can be due to various causes like anatomical defect of uterus, chromosomal abnormalities, endocrinal imbalances, subclinical infections and immunological disturbances. The immune factors are classified as autoimmune and all immune. One of the most important immunological cause for the fetal loss is antiphospholipid (APL) antibodies, resulting from autoimmune factors.
Antiphospholipid Syndrome (APS) is an autoimmune disorder characterized by a high-risk of obstetrical complications affecting both mother and fetus. Current clinical Antiphospholipid Syndrome (APS) criteria include early delivery, oligohydramnios, neonatal complications such as prematurity, intrauterine growth restriction (IUGR), fetal distress and rarely fetal or neonatal thrombosis, associated maternal obstetric complications like pre-eclampsia/eclampsia and HELLP syndrome, arterial or venous thrombosis and other aPL-related complications like placental insufficiency [2]. Antiphospholipid antibodies are a family of approximately 20 antibodies directed against negatively charged phospholipid binding proteins. However, only the LA and aCL (IgM and IgG subclass but not IgA),

have been shown to be of clinical significance [3].
The prevalence of APL is estimated to be 5% of the general population, and APS represents 0.5%. However, APL is commonly found in 15% of women with recurrent pregnancy losses (RPL), suggesting that APS is one of the most frequent acquired aetiology for RPL [4].

Aims and Objectives

1. To investigate the association of antiphospholipid antibodies in women with bad obstetric history and thus evaluating the usefulness of routine screening for serum antiphospholipid antibodies in patients with history of unexplained fetal wastage and bad obstetric history for better outcome.
2. To know the benefits of anticoagulants in these APLA positive patients.

Materials and Methods

The study was conducted in the Department of Obstetrics & Gynaecology at SDM College of Medical Science and Hospital, Dharwad, India, over a period of 1 year from November 2015 to October 2016, involving 57 women with Bad Obstetric History satisfying the inclusion and exclusion criteria, after atleast 12 weeks from their last pregnancy/miscarriage and were subjected to APLA screen and retested after 12 weeks.

Inclusion criteria

1. Women of age group 18-35 years
2. Women with bad obstetric history(2 or more first trimester miscarriages, patients with one or more second trimester miscarriages and those with pregnancy losses less than 34 weeks due to severe pre-eclampsia, IUGR, abruption and unexplained intra uterine death).
3. Regular normal menstrual cycles

Exclusion criteria

1. Women >35 years of age
2. History of diabetes mellitus, thyroid disease or any other chronic medical illness
3. Congenital anomalies in the fetus

This study was approved by the Research Ethics Committee of the college and a written and informed consent was obtained from the patients after thorough counselling about the test, its implications, future treatment and follow up if test results were positive. Detailed information regarding socio-demographic factors, detailed previous pregnancy history-their gestational age, pregnancy losses, any congenital anomalies, complications during antenatal period like severe pre-eclampsia, IUGR and abruption remote from term, weight of fetuses and investigation results were collected. After which a complete general and gynaecological examination was done and under aseptic precautions venous blood was withdrawn and tested for APLA syndrome especially lupus anticoagulant assay, Anti- cardiolipin IgG/IgM and Anti Beta2 glycoprotein (β2-GP1) 1 IgG/IgM. Those who were tested positive were retested 12 weeks later to confirm the result.
The results categorized the study population into cases (those who tested positive for APLA) and comparison group (those who tested negative for APLA). The data collected was entered into Microsoft excel spread sheet and analysed using IBM SPSS Statistics, Version 22(Armonk, NY: IBM Corp). Comparison of the categorical variables between the study groups was performed using the Chi square test and Fishers test. Comparisons of the categorical variables at two time intervals was done using Mc Nemar test. P value < 0.05 was considered as statistically significant.

Results

A total of 57 women with bad obstetric history were recruited in the study. Among 57 total cases 40 were found to be APLA negative and 17 cases were APLA positive. The tests were repeated for the positive samples 12 weeks later. Repeat testing revealed 3 samples to be LA negative and 2 samples for IgG and IgM of β2-Glycoprotein 1 as negative. After testing for the second time, there were total 2 positive Anticardiolipin antibodies IgM samples (16.6%), 8 samples were Lupus anticoagulant positive (66.6%) and 1 was positive for β2-Glycoprotein 1 antibodies IgG and IgM each (8.3%) making a total of 12 (21%) APLA positive cases (Table 1).

Table 1: Distribution of individual APLA antibodies at baseline and repeat after 12 weeks.

APLA Antibodies	Positive Results	Repeat test >12 weeks (Negative result)	Total (Percentage %)
ACL IgG	0	0	0 (0)
ACL IgM	2	0	2 (16.6)
β2-GP1 IgG	2	1	1 (8.3)
β2-GP1 IgM	2	1	1 (8.3)
LA	11	3	8 (66.6)

ACL: Anticardiolipin, LA: Lupus Anticoagulant, β2-GP1 Anti Beta2 glycoprotein:

Table 2 shows age distribution of APLA positive and negative cases. 7 cases of APLA positive were below 25yr age group and 5 cases were above 25yr age group.

Table 2: Age distribution APLA negative and positive test.

APLA	Age in years		Total
	<25years	>25 years	
Positive	7	5	12
Negative	20	27	47
Fisher's exact test	p-value = 0.49		

In the study, 35 patients had history of more than two miscarriages, including 4 patients with second trimester loss. Preeclampsia and associated complications were seen in 6 patients. There were 12 cases of intrauterine deaths with unknown etiology and 1 case of intrauterine growth restriction. Vascular thrombotic complication was present in 3 cases, out of which 1 case was detected to be APLA positive. Rheumatoid arthritis was seen in 3 of the total cases and 1 patient was found positive for APLA (Table3).

Table 3: Comparison of magnitude of various criteria of BOH in study population

Past complication	APLA		Total
	Negative	Positive	
Recurrent pregnancy loss (>2 miscarriages)	27	8	35
Early onset preeclampsia/eclampsia	6	0	6
IUGR	1	0	1
IUD	9	3	12
Vascular thrombotic complications	2	1	3
Association with rheumatoid arthritis	2	1	3

IUGR: Intrauterine Growth Restriction, IUD: Intrauterine Death

Among 57 cases, 45 patients had complications in the past pregnancy and 26 patients had complications in the present pregnancy. There were 15 cases in the study who had past complications and presented with complication during the current pregnancy. Most of the patient s (23) presented with the hypertensive complications, 14 cases were associated with unexplained intrauterine deaths, 9 women had intrauterine growth restriction and 2 cases manifested with abruption (Table4).

Table 4: Distribution of present complications in the study.

Present complications	APLA		Total
	Positive	Negative	
Recurrent pregnancy loss	0	1	1
Early onset preeclampsia/eclampsia	2	21	23
IUGR	2	7	9
IUD	2	12	14
Abruption	0	2	2

IUGR: Intrauterine Growth Restriction, IUD: Intrauterine Death

Among 12 APLA positive cases, 8 were started on LMWH and 3 APLA negative patients were also on Heparin due to other risk factors which included previous history of cortical vein thrombosis or other thrombotic complications. The patients continued Heparin and the outcomes were analysed (Table 5).

Table 5: Distribution of cases started on Heparin treatment

		APLA		Total
		Positive	Negative	
LMWH	Yes	8	3	11
	No	2	44	46

A total of 36 women conceived during the study and delivered. There were total 12 (33.3%) cases who underwent LSCS, 18 (50%) patients underwent preterm vaginal deliveries and 6 (16.7%) cases underwent full term vaginal deliveries. Out of 12 patients undergoing LSCS, 4 cases were APLA positive and 8 were APLA negative. 2 cases undergoing full term vaginal deliveries were APLA positive.2 APLA positive cases underwent preterm vaginal delivery. The most common cause of preterm vaginal delivery being spontaneous preterm labour and early inductions due to preeclampsia and its complications. The difference in the outcome of the 2 groups was not statistically significant (Table 6).

Table 6: Mode of delivery in the two groups

Mode of delivery	APLA		Total
	Positive	Negative	
FTVD	2	4	6
LSCS	4	8	12
PTVD	2	16	18
Fisher's exact test	p-value = 0.24(NS)		

Out of the 36 deliveries, there were total of 9 intrauterine deaths out of which 2 belonged to APLA positive mothers. 5 new born out of 13 belonged to APLA positive group and were shifted to mother side. Total of 9 neonates were shifted to NICU, prematurity being the most important cause and 6 had early neonatal deaths there was one twin preterm delivery in the study (Table 7).

Table 7: Neonatal outcome in the two groups

Neonatal outcome	APLA		Total
	Positive	Negative	
NICU admission	2(22.8%)	7(77.8%)	9
Mother side	5(38.5%)	8(61.5%)	13
IUD	2(22.8%)	7(77.8%)	9
Early neonatal deaths	0	6(100.0%)	6
Fisher's exact test	p-value = 0.38		

Discussion

In the present study of 57 cases with bad obstetric history (BOH), 12 cases were found to be APLA positive giving a prevalence of 21%. The reported prevalence of APLA positivity in literature is 6-8% in the general population, whereas in high risk women with bad obstetric history it is 10-46% [5, 6, 7].

Anticardiolipin antibodies seem to be better predictors of the fetal outcome. In the current study the overall Anticardiolipin antibodies positive cases were 3.5% which was much less to the other studies where anticardiolipin antibodies are seen in 8-40% of the cases [8, 9]. Lupus anticoagulant antibodies are studied to cause thrombosis in the maternal circulation leading to fetal loss. The positivity for Lupus Anticoagulant in our study was 14.03% which was higher as compared to the studies by J. Zolghadri *et al*, and Festin *et al*. who found the prevalence of LA as 8.7% and 7% respectively [10, 11].

APS causes a pro-thrombotic, pro-inflammatory state in the parturient, resulting in thrombosis, pregnancy loss, and problems related to placental insufficiency. Our results also imply greater risk of preeclampsia, preterm births, intrauterine growth restriction and neonatal deaths in women with antiphospholipid antibodies [2]. In our study group the patients presented with complicated obstetric history of previous recurrent pregnancy loss, early onset preeclampsia or its complications, unexplained intrauterine deaths, intrauterine growth restriction, abruption, vascular thrombotic complications and association with rheumatoid arthritis. We divided these complications as past and present. Early pregnancy loss with history of more than 2 miscarriages was seen in 36 patients and 8 (22.2%) cases were positive for APLA. In our study 29 cases had past or present history of preeclampsia and its complications and only 2 were associated with APLA positive. Lt Col Singh G *et al* found that 17.72% patients with BOH had preterm deliveries and 20.25% of patients developed preeclampsia, these were found to be statistically significant factors in BOH group [7]. These findings are comparable to findings from our study. Our study also

included 3 patients with the history of thrombotic complications in the form of deep venous thrombosis and cortical venous thrombosis. One patient with 5 recurrent miscarriages had history of deep venous thrombosis and she was Lupus anticoagulant positive with high titres requiring Heparin therapy. Thus Lupus anticoagulant is consistently the most powerful predictor of thrombosis.

There was no statistically significant difference in the mode of delivery and neonatal outcome in the two groups. Most of the preterm vaginal deliveries were spontaneous preterm or induced labour due to preeclampsia and its complications. Neonatal intensive care admissions were either due to prematurity or respiratory distress. We had 9 cases of Intrauterine deaths in which 2 were APLA positive. The cause of intrauterine death was explained by fetal hypoxia due to reduced placental perfusion, hypertensive disorders or abruption. Gonen *et al* studied the association between women with APS and unexplained intrauterine fetal death as compared to controls after 26 week of gestation and found that the Lupus anticoagulant and anticardiolipin antibodies were significantly more prevalent in women with IUD [12]. There were 6 early neonatal deaths of APLA negative mothers in the study either due to prematurity or sepsis.

Guidelines for first-line APS treatments during pregnancy vary between countries. However, combination of low-dose aspirin (LDA) and LMWH injections is usually accepted and improves both fetal and mother outcome. Thus, without treatment, the chances of successful pregnancy are around 30%, 50% with LDA alone, and up to 70% with both molecules [13]. In our study 8 out of 12 APLA positive cases were started on Heparin. The other 2 APLA positive patients were lost to follow up. The patients continued Heparin and the outcomes were analysed. We found that there was statistically significant difference between the patients who continued Heparin in APLA positive cases as compared to APLA negative cases. R. Rai *et al* concluded in their study that the treatment with Aspirin and Heparin resulted in significantly higher rates of live births in the APLA positive women with history of recurrent miscarriages [14].

Conclusion

The antiphospholipid antibodies have been the most important cause for recurrent fetal loss thus many pregnancies can be saved if diagnosed and treated adequately. This can be done by routine screening for the antiphospholipid antibodies in a pregnant women with a bad obstetric history and unexplained fetal loss. The outcome of high risk pregnancies in APLA syndrome is considerably improved by initiation of therapies using aspirin, unfractionated heparin and/ or low molecular weight heparin. APS pregnancies are real challenges for clinicians, require careful counselling, and multidisciplinary management is the key to a successful pregnancy.

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