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Study of Antiphospholipid syndrome in patients with bad obstetric history: A cross sectional study

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Abstract
Aims and Objectives: To look for Antiphospholipid Antibody Syndrome in patients with Bad Obstetric History and to assess the correlation between anticardiolipin antibodies and bad obstetric history.
Materials and Methods: This study was an Observational type of Cross sectional study carried out on 130 patients with Bad Obstetric History in non-pregnant state in Gynecology OPD of tertiary care centre, SDMH, Jaipur for one year (1st May 2015 to 30th April 2016). The patients were tested for APLA screen after atleast 12 weeks from their last pregnancy/miscarriage and were reassessed after 12 weeks. Depending upon the results the prevalence of APLA positivity was calculated and especially Anticardiolipin antibody positivity was studied. The results categorized the study population into cases (those who tested positive for APLA) and comparison group (those who tested negative for APLA) which were further studied regarding their obstetric history.
Results: The prevalence of Antiphospholipid Syndrome in patients with Bad Obstetric History was found to be 27.69% while the prevalence of Anticardiolipin antibodies was 18.46% and fetal loss at <10 weeks of gestation was found to be the most common type of pregnancy loss amongst BOH patients and patients with APS. (83.08% and 75% respectively).
Conclusion: The prevalence of Antiphospholipid antibody syndrome in patients with Bad Obstetric History is about 27.69% and the prevalence of Anticardiolipin antibodies alone contributes about 18.46%. Hence, all women with recurrent miscarriages should be screened before pregnancy for antiphospholipid antibodies, where all the conventional causes of miscarriages have been ruled out.

Keywords: Bad obstetric history, recurrent pregnancy loss, Antiphospholipid syndrome, Antiphospholipid antibodies, Anticardiolipin antibodies

Introduction

Pregnancy loss is a frustrating and challenging problem for couples and clinicians alike. Miscarriage is often associated with guilt, embarrassment and depressive states. The emotional issues surrounding pregnancy loss become magnified exponentially when miscarriage occurs on a repetitive basis. When evaluation of woman for recurrent pregnancy loss is done, an underlying contributing factor can be identified in 40-50%. If a contributing factor is found and treated, the prognosis for successful pregnancy outcome is typically around 80% [1]. A woman is said to have 'bad obstetric history (BOH)' if she has experienced any of the following events on two or more occasions in the past:

- Consecutive spontaneous abortions.
- Early neonatal deaths
- Stillbirths
- Intrauterine fetal deaths
- Intrauterine growth retardation
- Congenital anomalies in the fetus.

However, it is the occurrence of three consecutive pregnancy losses that constitutes the classic definition of BOH. This condition is seen in 1-2% of couples [2].
RCOG Guidelines [3] defines recurrent miscarriage as the loss of three or more consecutive pregnancies, however, The Practice Committee of the American Society for Reproductive Medicine [4] defines recurrent pregnancy loss as two or more failed pregnancies. For any given pregnancy, the reported risk of pregnancy loss is 15% and the likelihood of consecutive three losses, would be 0.34% [5]. There are 2 major reasons for recurrent spontaneous abortions. Either there is something wrong with the pregnancy itself, such as chromosomal abnormality that prohibits the pregnancy from implanting/ growing properly or there is a problem within the environment in which the pregnancy grows [6].

In view of the high incidence of spontaneous recurrent abortions of unknown cause, the continuous search for the etiology remains important.

The immune factors associated with pregnancy loss are classified as autoimmune and alloimmune factors. The autoimmune factors include the synthesis of auto-antibodies (antiphospholipid antibodies, antinuclear antibodies & anti thyroid antibodies). The viscosity of blood slightly increases during pregnancy, but in some women the blood is found to clot more easily due to the presence of certain antibodies called antiphospholipid antibodies. These blood clots in the placental blood vessels may decrease the blood flow to the baby resulting in miscarriage [7]. Obstetric manifestations of APS are not restricted to fetal loss. Current APS criteria include early delivery, oligohydramnios, neonatal complications (such as prematurity-estimated at 0-60% and more common in SLE patients, intrauterine growth restriction-IUGR-fetal distress and rarely fetal or neonatal thrombosis), associated maternal obstetric complications (like pre-eclampsia/eclampsia and HELLP syndrome-hemolytic anemia, elevated liver enzymes, and low platelet counts, arterial or venous thrombosis) and other aPL-related complications (placental insufficiency) [8]. 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 subcalss but not IgA), have been shown to be of clinical significance [9].

Aims & Objectives

- To look for Antiphospholipid Antibody Syndrome in patients with bad obstetric history.
- To assess the correlation between anticardiolipin antibodies and bad obstetric history.

Materials and Methods

The study was conducted in the Department of Obstetrics & Gynaecology at Santokba Durlabhji Memorial Hospital, Jaipur from May 2015 to April 2016, on 130 non pregnant women with Bad Obstetric History satisfying the criterias mentioned, after atleast 12 weeks from their last pregnancy/miscarriage and were subjected to APLA screen and reassessed after 12 weeks.

After obtaining a written informed consent, detailed history and complete general and gynecological examination was done and under aseptic precautions venous blood was withdrawn. Depending upon the results the prevalence of APLA positivity was calculated and especially Anticardiolipin antibody positivity was studied. The results categorized the study population into cases (those who tested positive for APLA) and comparison group (those who tested negative for APLA) which were further studied regarding the demographic profile, obstetric history etc.

Inclusion criteria

1. Women of age group 18-35 years
2. Women with bad obstetric history; with 2 or more adverse pregnancy outcome [4]
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 uterine anomalies
4. Presence of any infections (including TORCH)
5. Obese women (BMI>/=30)
6. Personal habits of smoking, alcohol or any substance abuse.

Serum levels of anticardiolipin (IgG & IgM) were measured & repeated after 12 weeks using AESKULISA phospholipid-screen-GM (Germany) which is a solid phase for the separate qualitative & quantitative detection of IgG and /or IgM antibodies in human sera. Diluted serum samples were incubated in microplates coated with the specific antigen. Patient's antibodies, if present in the specimen, bound to antigen. The unbound fraction got washed off in the following step.

Results were expressed in GPLU/mL:

- Normal <12 GPLU/mL
- Borderline 12-18 GPLU/mL
- Positive >18 GPLU/mL

For determination of Lupus Anticoagulants plasma samples were identified in a stepwise fashion. The activated partial thromboplastin time (APTT) was determined with a commercial thromboplastin (Actin FSL, American Dade, Aguada, and Puerto Rico) in 1:4 mixtures of pooled: patient plasma. Specimens was considered abnormal when the APTT exceeded 37.1 seconds (mean +2 SD for the 20 normal plasma samples). The dilute Russell's viper-venom time (dRVVT) was determined in 1:1 mixtures of pooled: patient plasma. The venom and the phospholipid (Thrombofax, Ortho Diagnostic Systems, and Raritan, N. J) was diluted to concentrations of 1:200 and 1:32, respectively. Specimens was considered abnormal when the dRVVT exceeded 27.5 seconds (mean +2 SD for the 20 normal plasma samples). Specimens shown to be abnormal by either test was also tested according to the platelet neutralization procedure, with use of a reagent from Bio Data (Hatboro, Pa). The results of this test was considered abnormal if the clotting time determined with the reagent was five or more seconds shorter than the time determined in parallel in the same sample with the use of 150 mM sodium chloride. In summary, plasma samples shown to have an abnormal APTT or dRVVT on testing of standardized mixtures of pooled: patient plasma, as well as an abnormal clotting time on testing with the platelet neutralization procedure and no evidence of heparin or fibrin-fibrinogen degradation products, was considered positive for lupus anticoagulants.

The Anti-Beta 2 Glycoprotein Antibody (IgG & IgM) were measured using the ELISA principle (Enzyme Linked Immunosorbent Assay). In this the highly purified native antigen, human beta 2 glycoprotein is bound to the solid phase and the specific immunoglobulins bind to the antigen through incubation through diluted human serum. After washing, incubation was performed with the conjugate composed of antihuman immunoglobulins and horse radish peroxidase. The color which developed was proportional to the concentration of specific antibodies present in the serum sample.

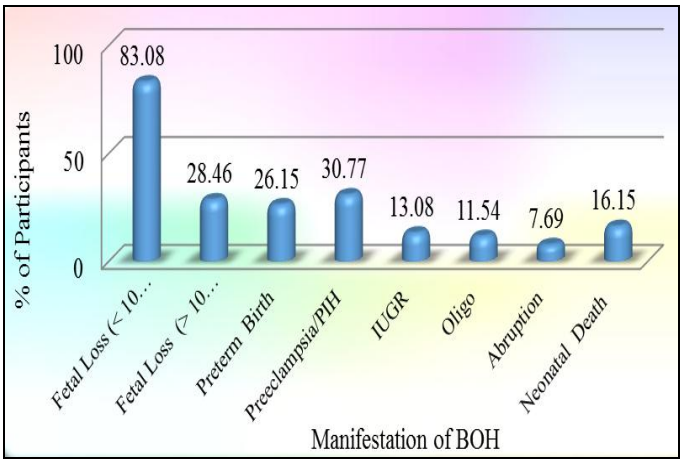
Results were expressed as AU/mL:

- Normal <12 AU/mL
- Borderline 12-18 AU/mL
- Positive >18 AU/mL

Results and Observations

Table 1. Comparison of magnitude of various criteria of BOH in study population

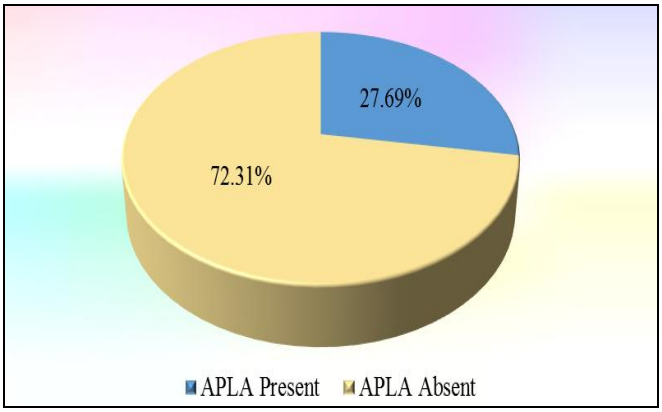
BOH (N=130)	No.	%
Fetal loss (<10 weeks)	108	83.08
Fetal loss (>10 weeks)	37	28.46
Preterm birth(<34 weeks)	34	26.15
Pre eclampsia/PIH	40	30.77
IUGR	17	13.08
Oligo	15	11.54
Abruption	10	7.69
Early Neonatal death	21	16.15



Graph 1. Comparison of magnitude of various manifestations of BOH in study population

Table 2. Prevalence of Antiphospholipid Syndrome in patients with BOH

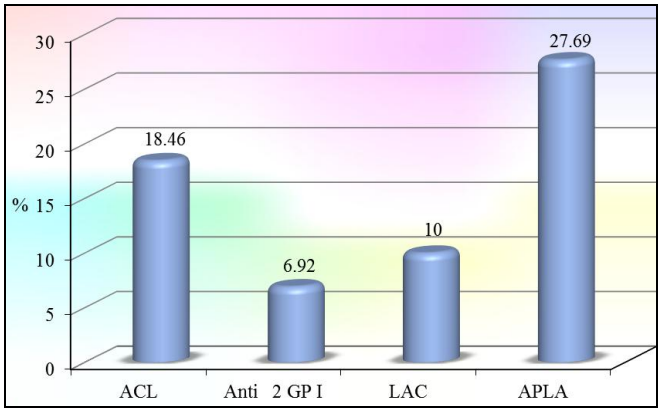
Antiphospholipid Syndrome	No.	%
Present	36	27.69
Absent	94	72.31
Total	130	100



Graph 2. Prevalence of Antiphospholipid Syndrome in patients with BOH

Table 3. Prevalence of various antiphospholipid antibodies in BOH patients

Antibody	No.	%
ACL	24	18.46
Anti β2 Glp	9	6.92
LAC	13	10.00
APLA	36	27.69
Total BOH patients	130	100



Graph 6. Prevalence of various antiphospholipid antibodies in BOH patients

Table 4. Prevalence of IgG and IgM type of ACL & β2 Glycoprotein antibodies

	ACL Ab		β2 Glp Ab	
	No.	%	No.	%
IgG	18	13.85	6	4.62
IgM	13	10.00	5	3.85
Both	7	5.38	2	1.54
Total	24	18.46	9	6.92

Table 5. Comparison of magnitude of various criteria of BOH with respect to Antiphospholipid antibody status

BOH	APLA				'p' Value*
	Negative (N=94)		Positive (N=36)		
	No.	%	No.	%	
Fetal loss (<10 weeks)	81	86.17	27	75.00	0.208
Fetal loss (>10 weeks)	26	27.66	11	30.56	0.912
Preterm birth	22	23.4	12	33.33	0.353
Pre eclampsia/PIH	25	26.6	15	41.67	0.146
IUGR	9	9.57	8	22.22	0.105
Oligohydroamnios	10	10.64	5	13.89	0.832
Abruption	3	3.19	7	19.44	0.006
Early neonatal death	14	14.89	7	19.44	0.715

Chi-square test

Table 6. Distribution of BOH patients according to APLA status and assisted or spontaneous conception

Conception	APLA				Total	
	Negative		Positive			
	No.	%	No.	%	No.	%
Assisted	9	9.57	6	16.67	15	11.54
Spontaneous	85	90.43	30	83.33	115	88.46
Total	94	100.00	36	100.00	130	100.00

Chi-square = 0.682 with 1 degree of freedom; P = 0.409

Table 7. Distribution of BOH patients according to APLA status and previous h/o thromboembolic episodes

Previous Thromboembolic Episodes	APLA				Total	
	Negative		Positive			
	No.	%	No.	%	No.	%
No	94	100.00	30	83.33	124	95.38
Yes	0	0.00	6	16.67	6	4.62
Total	94	100.00	36	100.00	130	100.00

Chi-square = 12.857 with 1 degree of freedom; P <0.001

Table 8. Distribution of BOH patients according to APLA status and primary or secondary RPL

Primary/Sec RPL	APLA				Total	
	Negative		Positive			
	No.	%	No.	%	No.	%
Primary	78	82.98	30	83.33	108	83.08
Secondary	16	17.02	6	16.67	22	16.92
Total	94	100.00	36	100.00	130	100.00

Chi-square = 0.045 with 1 degree of freedom; P = 0.831

Table 9. Distribution of BOH patients according to presence of number of various APL (ACL/LAC/Anti β2 Glycoprotein) antibodies

Positivity	No.	%
Absent Ab	94	72.31
Single Ab	26	20.00
Double Ab	10	7.69
Triple Ab	0	0
Total	130	100.00

Table 10. Comparison of magnitude of various BOH factors with respect topresence of number of various APL (ACL/LAC/Anti β2 Glycoprotein) antibodies

BOH	APLA Positivity						'p' Value*
	Negative (N=94)		1 Positive (N=26)		2 Positive (N=10)		
	No.	%	No.	%	No.	%	
Fetal loss(<10 weeks)	82	87.23	20	76.92	7	70.00	0.209
Fetal loss(>10 weeks)	24	25.53	7	26.92	4	40.00	0.643
Preterm birth (<34 weeks)	22	23.40	8	30.77	4	40.00	0.439
Pre eclampsia or PIH	25	26.60	10	38.46	5	50.00	0.199
IUGR	9	9.57	6	23.08	2	20.00	0.155
Oligohydroamnios	10	10.64	4	15.38	1	10.00	0.789
Abruption	3	3.19	4	15.38	3	30.00	0.003
Neonatal death	14	14.89	5	19.23	2	20.00	0.818
Live births	18	19.15	6	23.08	4	40.00	0.306
Prev. thromboembolic episodes	0	0.00	4	15.38	2	20.00	0.000
Assisted Conception	9	9.57	5	19.23	1	10.00	0.390
Primary RPL	78	82.98	22	84.62	8	80.00	0.946
Secondary RPL	16	17.02	4	15.38	2	20.00	

Chi-square test

- The prevalence of Antiphospholipid Syndrome in patients with Bad Obstetric History was found to be 27.69% while the prevalence of Anticardiolipin antibodies was 18.46%.
- The prevalence of Lupus Anticoagulants in BOH patients was 10% and that of β2 Glycoprotein Antibody was 6.92%.
- Fetal loss at <10 weeks of gestation was found to be the most type of pregnancy loss amongst BOH patients and patients with APS. (83.08% and 75% respectively)
- Ig G type of antibodies (of both ACL and β2 Glycoprotein antibodies) were more prevalent than Ig M type of antibodies in APS patients.
- In APLA positive patients fetal losses >10 weeks was present in about 30.56% patients and 33.33% patients had preterm deliveries while preeclampsia was noticed in 41.67% of patients.
- About 16.67% patients with APLA positivity had history of assisted reproduction and hence showed some sort of subfertility/infertility.
- 16.67% of patients had h/o thromboembolic episodes in the past (therefore had secondary APS). This association was statistically significant.
- 83.33% of APLA positive patients had no live issue and hence had primary recurrent pregnancy loss.
- 20% of BOH patients showed positivity for single antibody only while 7.69% patients showed positivity for at least 2 different types of APL antibodies. No patient showed positivity for triple antibodies.
- With presence of more than one type of antibody the chances of having fetal losses at later weeks of gestation, developing pre eclampsia, preterm births and abruptions increased though not in a statistically significant manner.

Discussion

In our study 83.08% patients with BOH had fetal loss at <10 weeks of gestation which is similar to the findings of Franklin RD *et al* [10] who found that 90% of the pregnancy losses occurred before 12 weeks of gestation and finding of Ismail A E D M *et al* [9] who found that almost 85% of women with RPL had pregnancy losses mainly in 1st trimester and some in 2nd trimester. Lt Col Singh G *et al* [1] found that 17.72% of

patients with BOH had preterm deliveries and 20.25% of patients developed PIH & these were found to be statistically significant factors in BOH group. These findings are comparable to our findings (26.15% preterm; 30.77% PIH).The prevalence of Antiphospholipid Syndrome in patients with BOH in our study was 27.69%. Our findings are similar to the findings of Ghosh A *et al* [11] (prevalence of APLA = 27.7%) The prevalence of Anticardiolipin antibodies (IgG/IgM), Lupus anticoagulants and B2 Glycoprotein antibodies (IgG/IgM) were recorded as 18.46%, 10% and 6.92% respectively. In our study we found that Ig G type of antibodies were more prevalent than IgM type of Ab such that 13.85% patients were IgG Ab positive, while only 10% were IgM positive. Our findings are in agreement with findings of studies [8, 9]. Anticardiolipin IgG antibodies seem to be better predictors of the fetal outcome although the presence of IgM antibodies is not without risk to the fetus. 16.67% of BOH patients with APLA positive status had to take medical assistance for conceiving & hence showed some component of subfertility though this was not statistically different.Di Prima FAF [8] also suggested a probable relationship of aPL to infertility and also found that aPL antibodies are increased in patients undergoing *in vitro* fertilization (IVF). Buckingham KL *et al* [12] also found that infertile women, and those with recurrent IVF implantation failure, have an increased incidence of aPL (22% and 30%, respectively) compared with a healthy, fertile population (1-3%). Their findings support our findings. 16.67% of APLA positive patients had h/o thromboembolic episodes in the past (therefore had secondary APS) while no patient with APLA negative status had such history; the difference being highly statistically significant (p<0.001). Our findings are in agreement with the findings of Cervera R *et al* [13] who also found that recurrent thrombotic events appeared in 16.6% patients with APS and the most common were strokes (2.4% of the total cohort), transient ischaemic attacks (2.3%), deep vein thromboses (2.1%) and pulmonary embolism (2.1%).

Conclusion

This study shows that the prevalence of Antiphospholipid antibody syndrome or the APS in patients with Bad Obstetric History is about 27.69% and the prevalence of Anticardiolipin antibodies alone contributes about 18.46%. All women with recurrent first-trimester miscarriage and all women with one or more second trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies where all the conventional causes of miscarriages have been ruled out and this in agreement with Royal College of Obstetricians and Gynecologists (RCOG) 2011 recommendations for the investigation of couples with recurrent pregnancy loss [3].

Our study also suggests that conventional APA assays (LA and ACA) are effective in the detection of a majority of APA positive cases and by the addition of other cofactor dependent (β2 GP1) APA assay, there is a considerable increase in the diagnostic efficiency in the detection of APA.

APS causes a pro-thrombotic, pro-inflammatory state in the parturient which puts her at risk for thrombosis, pregnancy loss, and problems related to placental insufficiency. Our results also imply greater risk fetal losses, preterm births, preeclampsia and neonatal deaths in women with antiphospholipid antibodies.

The limitation of this study is similar to the limitations of all cross-sectional studies. As there is a need for prospective long-term well-controlled cohort studies, investigating all possible cause of recurrent pregnancy loss, with particular reference to antiphospholipid antibody syndrome.

Treatment includes lifelong anticoagulation in a case of thrombosis, whereas for isolated obstetric APS, prophylactic heparin is given in pregnancy. Low dose aspirin is often added to both regimens. APS remains an exciting area for research and encompasses all areas of medicine-presenting as young stroke to a neurologist, venous thrombosis to an internist, poor obstetric history to an obstetrician, valvular disease or myocardial infarctions to a cardiologist

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