Estimation of Antiphospholipid Antibodies, Anticardiolipin Antibodies, Beta-2 Glycoprotein 1 Antibodies in Recurrent Pregnancy Loss - A Case-control Study

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ABSTRACT

Introduction: Recurrent miscarriage is the occurrence of three or more consecutive pregnancy loss before 20 weeks of gestation. Antiphospholipid Antibodies (APAs) are one of the causes responsible for recurrent pregnancy loss.

Aim: Estimation of APAs, Anticardiolipin Antibodies (ACAs) and Beta-2 Glycoprotein 1 Antibodies (β-2 GP1 Abs) in recurrent pregnancy loss and also to assess which antibody has strong correlation with habitual abortion patients.

Materials and Methods: This was a case-control study that included the total number of 45 women of reproductive age group from Obstetrics and Gynaecology Department, KGMU, Lucknow, Uttar Pradesh, India, out of which 30 women had been taken as case and 15 as control. Dilute Russell Viper Venom Test (DRVVT) was applied for Lupus Anticoagulant (LA) and Enzyme Linked Immunosorbent Assay (ELISA) for ACA, APA and β-2 GP1 Ab.

Result: Majority of cases showed higher positivity for β-2 GP1 Abs 11/30 (36.7%) with lesser positivity for ACA 4/30 (13.4%) and APAs 4/30 (13.4%). All the antibodies were absent in control group. Majority of cases showed positivity for β-2 GP1 Ab out of which two cases also showed positivity for ACA, APA and LA.

Conclusion: β-2 GP1 Abs are useful and a significant marker in recurrent pregnancy loss in women as compared to ACA and APAs.

INTRODUCTION

Recurrent pregnancy loss is also known as habitual abortion or recurrent miscarriage or recurrent abortion. Recurrent pregnancy loss is the occurrence of three or more pregnancies that end in miscarriage of the foetus, usually before 20 weeks of gestation. Recurrent pregnancy loss affects about 0.34% [1] of women and cause childlessness in 2-5% who are trying to conceive [2,3]. Common factors that cause recurrent abortions are uterine abnormalities (uterine septum, leiomyomata), cervical conditions (cervical incompetence), chromosomal abnormalities (balanced or Robertsonian translocation, aneuploid) [4], endocrine disorders (hypothyroidism, poorly treated diabetes mellitus, polycystic ovarian syndrome), Thrombophilia (factor V leiden), ovarian factors (luteal phase defect, reduced ovarian reserve), life style factors (smoking, alcohol, drugs), infections (syphilis, brucellosis) [4], immune factors, thyroid antibodies [5] and Antiphospholipid Syndrome (APS) [6]. APS has been considered known cause of recurrent pregnancy loss in 5 to 20% of women [6,7]. APS is an autoimmune disease in which abnormal proteins (antiphospholipid antibodies) form that attacks on phospholipid (lining of blood vessels) and after that clot or thrombus formation occur [8-10]. APS has triad of recurrent pregnancy loss, thrombosis and autoimmune thrombocytopenia [11,12]. APS is defined by laboratory parameters with presence of APAs (IgG and IgM), β-2 GP1 Abs (IgG and IgM), ACAs (IgG and IgM) and lupus anti-coagulant antibodies (IgG and IgM) [12-14]. APS is considered as an important autoimmune cause of various medical problem [15,16]. With regard to pregnancy loss, APS is an important diagnosis because treatment may improve subsequent pregnancy outcomes. Long term anticoagulation [17] were required in women with potential risk such as thrombosis in pregnancy [18,19]. It has

been found that ACA may be the cause of foetal loss in recurrent miscarriages with inflammatory response [20]. Beta-2 glycoprotein 1 acts as a natural anticoagulant [21] by obstructing the clotting activity of platelets [22]. It was found that antibodies to beta-2 glycoprotein 1 act as a prothrombotic in recurrent miscarriages [23]. Therefore, this study was done to assess the role of antiphospholipid antibodies viz., LA, ACAs IgG and IgM, and β-2 GP1 Ab IgG/IgM, in the patients of recurrent pregnancy loss and also to assess which antibody has strong correlation with habitual abortion patients.

MATERIALS AND METHODS

This was a retrospective case-control study done in Obstetrics and Gynaecology Department, King George's Medical University, Lucknow, Uttar Pradesh, India in collaboration with Department of Pathology during the period from June 2011 to August 2012 after clearance from Ethical Committee of Medical University. Total number of participants was 45 women out of which 30 women had been taken as case and 15 as control. Inclusion criteria of cases (Group 1) were women of reproductive age group (15-45 years) with history of three or more consecutive pregnancy loss up to 20 weeks of gestation and control (Group 2) of reproductive age group (15-45 years) with at least one successful pregnancy and no history of previous abortion. Exclusion criteria were women of same age group (15-45 years) with history of at least one or two abortions, history of still birth, history of intermittent pregnancy loss. Assessment of patients was done with requisition form that included- Patient name, age, gravida and parity, occupation, obstetrics history, date of last abortion and socioeconomic status.

Blood was collected in tri-sodium citrate vial from cases and controls for the evaluation of coagulation tests- Activated Partial

Thromboplastin Time (APTT), DRVVT (LA Screen and LA Confirm) with kit supplied by Tulip Diagnostics, Goa, India. ELISA test was performed by using serum for the study of APA IgG and IgM, ACAs IgG and IgM and β-2 GP1 Ab IgG/IgM.

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) version 15.0 was used for the data analysis. The following statistical tests were applied-mean, standard deviation, chi-square test, paired t-test, level of significance and p-value <0.05 considered as statistically significant.

RESULTS

In this study the results showed that each antibody was related with recurrent miscarriage women but in different ratio. LA tests-APTT and DRVVT, was positive in only 1/30 recurrent miscarriage women and negative in all control group 0/15. In both the group (case and control) p-value was not significant (p>0.05), so these tests have very minor importance in recurrent miscarriage women. In ELISA tests, all the three antibodies showed positive result but in different ratio. Both Anticardiolipin and antiphospholipid antibodies (IgM and IgG) showed positive result in only two cases, in this way these two antibodies also had very minor significance value in recurrent miscarriage women as shown in [Table/Fig-1-4]. There was strong positivity of β-2 GP1 Abs (IgM and IgG) in recurrent miscarriage women at a significant rate (p=0.017) as shown in [Table/Fig-5,6]. Eleven women out of 30 recurrent miscarriage women showed strong positivity for β-2 GP1 Abs. All the test parameters were negative in control group women. All the tests parameters were repeated after six weeks and there were no significant difference in result values as shown in [Table/Fig-7].

Statistically, no significant difference was observed in mean APTT of two groups though the mean value was higher in Group I as compared to Group II (p=0.201) as shown in [Table/Fig-8]. Mean DRVTT levels were higher in Group I as compared to Group II, and the difference was not statistically significant (p=0.071). DRVVT ratio (LA screen 7 LA confirm) were above the cut-off value >1.22 in only one case (positive for LA). None of the subjects had APTT levels above cut-off.

Mean ACA IgG levels were found to be higher in Group I as compared to Group II however, the difference was not found to be significant statistically (p=0.277) as shown in [Table/Fig-2]. Mean ACA IgM levels were found to be higher in Group I as compared to

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		Mean	SD	Mean	SD	"t"	*p
1.	IgM (MPL U/ml)	7.23	1.28	6.43	0.60	2.314	0.026
2.	IgG (GPL U/ml)	5.71	1.00	5.39	0.68	1.102	0.277

[Table/Fig-1]: Comparison of mean anticardiolipin antibody IgG and IgM levels between cases and controls.
mean, standard deviation, paired t-tests and level of significance *p-value

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		No.	%	No.	%	χ²	p-value
1.	IgM (>7 MPL U/mL)	2	6.7	0	0	1.047	0.306
2.	IgG (>10 GPL U/mL)	2	6.7	0	0		

[Table/Fig-2]: Distribution of subjects in two groups according to positivity status for anticardiolipin antibody IgG and IgM levels.
Chi-square tests and level of significance p-value

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		Mean	SD	Mean	SD	"t"	p-value
1.	IgM	7.69	1.54	7.89	0.50	0.495	0.623
2.	IgG	7.03	1.47	7.27	0.65	0.586	0.561

[Table/Fig-3]: Comparison of mean antiphospholipid antibody IgG and IgM levels between cases and controls.
Mean, standard deviation, paired t-tests and level of significance p-value

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		No.	%	No.	%	χ²	p-value
1.	IgM (>10 MPL/ml)	2	6.7	0	0	1.047	0.306
2.	IgG (>10 GPL/ml)	2	6.7	0	0	1.047	0.306

[Table/Fig-4]: Distribution of subjects in two groups according to positivity status for antiphospholipid antibody IgG and IgM levels.
Chi-square tests and level of significance p-value

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		Mean	SD	Mean	SD	"t"	p-value
1.	Beta-2 glycoprotein antibody	1.03	0.79	0.52	0.13	2.486	0.017

[Table/Fig-5]: Comparison of mean beta 2 glycoprotein 1 antibody between cases and controls.
mean, standard deviation, paired t-tests and level of significance p-value

S.No.	Positivity	Group I (n=30)		Group II (n=15)		Significance	
		No.	%	No.	%	χ²	p-value
1.	Negative (<1)	19	63.3	15	100		
2.	Borderline (1-1.4)	3	10.0	0	0	7.279	0.026
3.	Positive (>1.4)	8	26.7	0	0		

[Table/Fig-6]: Distribution of subjects in two groups according to positivity status for beta 2 glycoprotein 1 antibody (IgG/IgM).
Chi-square tests and level of significance p-value

S.No.	Parameters	Group I (n=30)		Group II (n=15)		Significance	
		Mean	SD	Mean	SD	"t"	p-value
1.	APTT	28.54	2.87	27.69	1.89	1.223	0.233
2.	DRVVT ratio	1.02	0.13	1.06	0.10	2.080	0.048
3.	Anticardiolipin antibody IgM	7.02	1.18	7.05	1.33	-0.220	0.827
4.	Anticardiolipin antibody IgG	5.74	0.95	5.24	1.14	2.325	0.028
5.	Beta-2 glycoprotein 1 antibody	0.978	0.80	0.916	0.62	1.203	0.240
6.	Antiphospholipid antibody IgM	7.61	1.46	7.65	1.34	-0.401	0.692
7.	Antiphospholipid antibody IgG	7.01	1.33	6.30	1.39	4.886	<0.001

[Table/Fig-7]: Comparison of mean values of all the test parameters at baseline and at follow up (in all the study subjects) (n=26).
Mean, standard deviation, paired t-tests and level of significance p-value

Group II and the difference between two groups was also found to be significant statistically (p=0.026).

ACA IgM and IgG levels were found to be above cut-off level in 2 (6.7%) subjects in Group I and no (0%) subject in Group II as shown in [Table/Fig-3]. However, the difference between two groups was not statistically significant.

Mean β-2 GP1 Ab levels were found to be higher in Group I as compared to Group II and the difference was found to be significant statistically significant (p=0.017) as shown in [Table/Fig-4].

In Group I, a total of 8 (26.7%) subjects were positive for beta-2 glycoprotein and 3 (10%) had borderline positivity, however, in Group II, none of the subjects were borderline or positive (p=0.026) as shown in [Table/Fig-5].

Mean APA IgG and IgM levels were found to be lower in Group I as compared to Group II however the difference was not found to be significant statistically (p>0.05) as shown in [Table/Fig-6].

APA IgM and IgG levels were found to be above cut-off level in 2 (6.7%) subjects each in Group I and no (0%) subject in Group II as shown in [Table/Fig-7]. However, the difference between two groups was not significant statistically.

A decrease in APTT and an increase in DRVVT were observed but the difference was significant only for DRVVT ratio (p=0.048) as shown in [Table/Fig-8]. An increase in mean ACA IgM levels and a decrease in mean ACA IgG levels was observed but it was significant only for ACA IgG (p=0.028) and not for ACA IgM (p=0.827). A decrease in mean β-2 GP1 Ab levels was observed but the change was not significant statistically (p=0.240). A decrease in mean APA IgG was observed which was also significant statistically (p<0.001). An increase in APA IgM was observed but the difference was not significant statistically (p=0.692).

S.No.	Variable	Group I (n=30)		Group II (n=15)		Significance	
		Mean	SD	Mean	SD	"t"	p-value
1.	APTT	28.27	3.08	27.07	2.55	1.299	0.201
2.	DRVVT Ratio	1.02	0.13	0.96	0.04	1.854	0.071

[Table/Fig-8]: Comparison of mean APTT, DRVVT and their ratio between cases and controls.
mean, standard deviation, paired t-tests and level of significance p-value

DISCUSSION

Antiphospholipid antibodies are a group of various antibodies such as LA, ACA, β-2 GP1 Abs, antiphosphatidylserine antibodies, antiphosphatidic antibodies, etc. Recurrent pregnancy loss is three or more consecutive pregnancy loss. Common factors that cause pregnancy loss are uterine abnormality, cervical incompetence, infections, autoantibodies, etc., [10,24]. The study included evaluation of APTT, LA, ACA IgG and IgM, Beta-2 GP1 Ab IgG/IgM and APA IgG and IgM in recurrent abortion or recurrent miscarriage with total 45 subjects in which 30 (66.7%) women of reproductive age group with history of three or more recurrent miscarriage (case study) and 15 (33.3%) women of same age group, with at least one living child without loss of any pregnancy (control study). The coagulation and ELISA tests were applied in all the subjects after six weeks and the results were approximately same.

LA also known as lupus antibody, LA, or lupus inhibitors, is an immunoglobulin (Joussen ATW et al.,) that binds to cell membrane (phospholipids and proteins) [24]. Jyotsna L et al., studied the association of various antibodies-LA, anticardiolipin antibodies, β-2 GP1 Ab and antiphospholipid antibodies with recurrent miscarriage and found that positivity of APA in 20% recurrent miscarriage women and LA in 16.6% recurrent miscarriage women [25], while Rajewski M et al., studied antiphospholipid antibodies, anticardiolipin antibodies in both recurrent miscarriage women and control group, they got antiphospholipid antibodies positivity in both recurrent miscarriage women and control group [26]. In this study LA was positive in only 1/30 recurrent miscarriage women and negative in all control group 0/15. In both the group (case and control) p-value was not significant (p>0.05). Study on LA in recurrent miscarriage women was done by Margaret D et al., and there were 14/29 (48%) study group women present positive status, they found 14/29 (48%) study group positive for LA [27]. Cardiolipin was found to be the key antigenic component of the Wassermann reaction [28]. It is a phospholipid present in mitochondrial membranes, and a much more sensitive immune assay [29]. In this study ACA IgM and IgG were found to be positive in 2/30 (6.7%) in recurrent miscarriage women and none of the subjects in control group showed positivity for ACA, 0/15 (0%) (p>0.05). Velayuthaprabhu S and Archunan G researched over anticardiolipin antibodies and antiphosphatidylserine antibodies and found that basic mechanism behind the recurrent pregnancy loss was ACA [30]. Mechanism behind antiphospholipid antibodies is that, clot or thrombus formation occurs in blood vessels which ultimately cause miscarriage [31].

Antiphospholipid autoantibody research was focused on phospholipid-binding proteins, rather than phospholipids themselves, with regard to pathophysiology and antibody specificity (Levine JS et al.,) [32]. In a prospective study done by Ghosh A et al., observed that recurrent miscarriage women showed 27.7% positivity for antiphospholipid antibodies [33]. In this study APA IgM and IgG were found to be positive in 2/30 (6.7%) in recurrent miscarriage women and no positivity in control group 0/15 (0%) (p>0.05). Akhlagi F et al., also demonstrated antiphospholipid/anticardiolipin antibodies in habitual abortion cases and the results were very different and they observed that recurrent miscarriage women showed positive result for only antiphospholipid antibodies and control group showed positivity for both antiphospholipid antibodies and anticardiolipin antibodies [34]. Song Y et al., performed study over recurrent miscarriage and APS and antiphospholipid antibodies titre and they had given treatment of low dose prednisone and aspirin few weeks before pregnancy in miscarriage women and APS patients. In the result they received low antibody titre than the previous level and no miscarriage occurred. They concluded in their research that beta-2 glycoprotein 1 IgM antibodies were the predominant form of APA in patients with recurrent miscarriage women and APS in this study [35]. Two theories have been proposed for the mechanism of Beta-2 GP1 Abs. First dimerisation theory in which one antibody bind to two beta-2 GP1 molecule (high density) to obtain considerable avidity (Arnout J et al., Lutters BC et al.,) [36,37]. Second hypothesis is based on the recognition of a cryptic epitope (exposed after binding of beta-2 GP1 to a negatively charged surface) (Wang SX et al., Merrill JT) [38,39] by antiphospholipid antibodies (Apl ab). In comprehensive analysis of anticardiolipin antibodies, β-2 GP1 Abs and LA in 430 women (habitual abortion cases), Vora S et al., assessed that prevalence value of ACA- 16.5%, β-2 GP1 Ab-5.4% and LA with ACA- 0.5% in cases (28) so conclusion was that every antibodies act as an independent risk factor [40]. Bao SH et al., also investigated the value of ACA and β-2 GP1 Ab in recurrent abortion patients at every 6 weeks with ELISA test and they evaluated that repeated and combined screening have more significance value (81.32%) rather than lesser screening [41]. Franklin RD et al., researched on β-2 GP1 Ab in habitual abortion patients with and without APS and they demonstrated that β-2 GP1 Ab have lesser significance in APS cases [42]. This study observed the higher positivity of β-2 GP1 Ab in 11 (36.7%) out of 30 recurrent miscarriage women (8=positive, 3=borderline) and only one case showed positivity for all antibodies -ACA (6.7%), APA (6.7%) and LA (3.35%). Few studies showed strong correlation of antiphospholipid antibodies in recurrent miscarriage women [25] and in few, both the group showed positivity [43]. Another study showed anticardiolipin antibodies positivity in few cases [44].

LIMITATION

The case control study has limitations because of small sample size and shorter follow up period. We could not assess other antibodies to rule out and also other disease like APS to differentiate these antibodies which we assessed.

CONCLUSION

Beta-2 glycoprotein 1 antibodies showed strong correlation with recurrent miscarriage. Other antibodies like antiphospholipid antibodies, anticardiolipin antibodies showed weak correlation with recurrent miscarriage women. Full workup with investigations can be initiated after two consecutive abortions to know the exact reason so that we could improve further pregnancy without fetal loss. Data of this study suggest that β-2 GP1 Abs should be included in the laboratory diagnosis of miscarriage women or in women having strong family history of miscarriage for better gestational result.

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