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Original Research Article

Prevalence and significance of thrombophilia markers in adverse pregnancy outcome

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ABSTRACT

Background: Thrombophilia complicates the pregnancy by interfering the physiology of utero-placental circulation which in turn leads to IUGR, IUD, PIH, RPL, abruption placentae. This study is to find out the prevalence and significance of different thrombophilia markers in cases of adverse pregnancy outcome in eastern part of Uttar Pradesh, India.
Methods: 54 antenatal women are selected from the cases presented with or previous history of PIH, IUGR, IUD, Abruption or early/late abortion. A thorough family history, history of risk factors, clinical examination were noted. Platelet count, prothrombin time(PT), activated partial thromboplastin time (APTT), plasma fibrinogen, factor-VIII assay, LA, ACLA, protein- C, protein- S, TORCH, thyroid profile, blood sugar, USG is done in all patients at the time of first registration. 50 antenatal females without any bad obstetric history was taken as controls.
Results: Among 54 cases, 64.8% cases were positive for thrombophilia markers, whereas 6% control had presence of thrombophilia markers. 6.5% thrombophilia positive cases had ≥3 markers present and had ≥2 manifestations of adverse pregnancy outcome in 100% cases. Prevalence of different thrombophilia markers are studied in individual case and association to various outcomes were noted.
Conclusions: There was high prevalence of thrombophilia markers in the cases with adverse pregnancy outcome. As treatment was found significantly effective in literature, screening of these markers should be done in patients with bad obstetric history.

Keywords: Adverse pregnancy outcome, Thrombophilia, Thrombophilia markers

INTRODUCTION

Thrombophilia is the propensity to develop thrombosis (blood clot) due to defect in several important proteins which are involved in the coagulation cascade. In India, the prevalence of thrombophilia and its association with adverse pregnancy outcome is high in different published studies. Two published studies, Vora et al in Maharashtra, found that 46.2% patient had any of the acquired thrombophilia while 37.5% had any of the heritable thrombophilia, combination of two or more genetic risk factors were 10.8% while genetic and acquired risk factors were 20.7%. Overall, 75.6% had either acquired, genetic or both forms of thrombophilia.[1]

Hossain et al, found 55% cases with acquired thrombophilia, 45% cases with inherited thrombophilia, 5% cases with combined thrombophilia.[2]

Mishra et al, Hossain et al concluded that APO collectively contributes to the largest population of maternal or fetal mortality and morbidity.[3,4] Kupferminc et al, Brenner B et al found that thrombophilic defects in 49% to 65% of women with adverse pregnancy outcome compared with 18% to 22%of women with normal pregnancy.[5,6] Mustafa et al suggested there appear to be an increased incidence of combined thrombophilic defect among the patient who presented with thrombosis.[7] Carriers of two defects seem to be at higher risk for thrombosis than their relatives with a single defect (Koeleman et al).[8] Similarly, Preston observed that presence of two or more thrombophilia markers increased the risk for pregnancy loss.[9]

There are several studies describing the associations of different thrombophilia markers with adverse pregnancy outcome. Kupferminc et al, Brenner et al found that thrombophilia positive patients have 3-8 fold increase in risk for recurrent pregnancy loss.[5,6] Vora et al also found protein S deficiency and presence of ACLA had strongest association (p value=<0.001 for each) with RPL.[1] The pooled odds ratio from a systematic review given by Alfirevic et al, they showed maximum Odds ratio 21.5 with protein C deficiency and PIH.[10]

Other significant association was with protein S deficiency and antithrombin deficiency. Yasuda et al found a relative risk of 26.6 (2.38 - 298.1) in cases with fetal death and ACLA.[11] Alfirevic Z gave association between still birth and various thrombophilia markers from the pooled odds ratio from 4 studies.[10] They got maximum association between protein S [OR = 16.2 (5 - 52.3)], ACLA [OR = 5.6(2.6 – 11.7)], LA [OR=3.2(1.2 - 9)]. Rey et al gave association between still birth and various inherited thrombophilia markers.[12] They got maximum association between protein S, prothrombin gene mutant, FVL. The strongest association of protein S in cases of stillbirth with Odd ratios 16.2. More or less same conclusion drawn by Robertson in a separate systemic review.[13] From the pooled odds ratios given by Alfirevic Z, abruption was mostly associated with ACLA and APC-R [odds ratio = 20.8 (2.5 - 175.8) and 6.6 (2.3 - 19) respectively].[10]

Rey showed the strongest positivity of anticardiolipin antibodies IgG (ACA IgG) in case of IUGR with an Odd Ratios 33.9, Yasuda et al, found a relative risk of 6.2 (2.43 - 16.0) in cases with IUGR and ACLA.[12] But this review was only on inherited thrombophilia.[11] This review found strongest association of protein-S deficiency with late miscarriage. Roque et al concluded that thrombophilia is not associated with early pregnancy loss.[14] In our study we observed that thrombophilia was associated with second trimester abortions (75%) where as thrombophilia negative cases were associated with first trimester abortions (70%) (Table 8). Vora et al found that ACLA, protein-S deficiency was associated with second trimester abortions (p value <0.001 each) but LA, protein-C deficiency was significantly associated with early pregnancy loss (p value <0.05 and 0.009 respectively).[1]

Thrombophilia is a potentially treatable cause of adverse pregnancy outcome. The purpose of screening is to determine who requires anticoagulation therapy. The objectives of the present study are:

- Prevalence of thrombophilia in cases of adverse pregnancy outcome
- Association of various thrombophilia markers (both inherited and acquired) in cases of adverse pregnancy outcome.

METHODS

The present study was carried out on 54 antenatal women presenting in the Department of Obstetrics and Gynaecology in Sir Sunderlal Hospital, Banaras Hindu University, Varanasi. It was carried out in collaboration with Department of Pathology, IMS, BHU.A protocol form was used to record the clinical and serological characteristics of the patients. The study was designed as a prospective case control study. We have used z statistics, P value, 95% confidence interval, and odd's ratio to validate the association of thrombophilia markers and adverse pregnancy outcome.

Criteria for selection of cases

The study population comprised of 54 antenatal women with age range of 20 - 37 years having presenting complaints of pregnancy induced hypertension, intrauterine growth restriction, intrauterine fetal death, abruptio-placentae, deep vein thrombosis. history of recurrent abortions

Criteria for selection of controls

A control population consisted of 50 women having without any adverse pregnancy outcome. No one of them had history of thrombosis.

Study group was subjected to following protocol

Detail history of previous pregnancy complications.

Investigations

- Routine blood and urine investigation
- Test to rule out other causes of adverse pregnancy outcomes including ultrasonography
- Screening coagulation test- PT, APTT, Factor VIII assay, Fibrinogen

- Test for thrombophilia markers - Blood for Lupus anticoagulant, IgG and IgM anticardiolipin antibodies, Protien S, Protien C, D-dimer.

Women in control group had tests for coagulation assay and thrombophilia markers.

RESULTS

64.8% (35/54) of cases were positive of thrombophilia markers, whereas 6% (3/50) of controls had presence of thrombophilia markers, (p value <0.001) (Table 1, 2).

Table 1: Prevalence of thrombophilia markers in the study group.

Markers	Case	%	Control	%
LA	13	24.07	1	2
ACLA	14	25.9	0	0
P-C DEF	10	41.6	1	2
P-S DEF	10	41.6	0	0
F-VIII	8	14.8	0	0
FIB	5	9.2	1	2
THR+VE	35	64.8	3	6
THR-VE	19	35.2	47	94

Note: Some of the cases had presence of more than one thrombophilia marker; those cases had been taken into account for more than one time.

In the study, 24.7% and 25.9% cases was positive for LA and ACLA (Acquired thrombophilia) respectively. Among the inherited thrombophilia markers i.e. protein C deficiency, protein S deficiency, excess factor VIII and fibrinogen were present in 41.6%, 41.6%, 12.9% and 7.4% of cases respectively. Only 6% of our control population was thrombophilia marker positive. But no more than one thrombophilia factor was observed in any of the controls (Table 1). This was in agreement with the study conducted by Vora et al.[1]

Table 2: Significance of thrombophilia factors with adverse pregnancy outcome.

Markers	Case	Control	P Value
LA	13	1	< 0.001
ACLA	14	0	< 0.001
P-C DEF	10	1	< 0.001
P-S DEF	10	0	< 0.001
F-VIII	7	0	< 0.001
FIB	4	1	< 0.001
THR+VE	35	3	< 0.001
THR-VE	19	47	< 0.001

Table 3: Distribution of study group according to the type of thrombophilia.

Type	Case	%
Inherited	14	25.9
Acquired	13	24.1
Combined	8	14.8
THR -VE	19	35.2

25.9% cases were positive for inherited thrombophilia, 24% cases were positive for acquired thrombophilia and 14.8% were positive for combined - acquired and inherited thrombophilia markers (Table 3).

Table 4: Association of thrombophilia markers with various adverse pregnancy outcome.

Markers	Abortion	PIH	IUD	IUGR	Abruption	DVT
LA	4	10 (29.4)	3 (33.3)	3 (21.4)	2 (40)	2 (66.7)
ACLA	6	10 (29.4)	1 (11.11)	4 (28.6)	0	2 (66.7)
P-C def	5	10 (29.4)	3 (33.3)	3 (21.4)	1 (20)	2 (66.7)
P-S def	6	7 (20.6)	1 (11.11)	3 (21.4)	2 (40)	1 (33.3)
FVIII excess	2	5 (14.7)	0	4 (28.6)	1 (20)	1 (33.3)
Fibrinogen excess	1	3 (8.8)	0	3 (21.4)	1 (20)	0
THR+VE	15	26	8	10	4	3
THR-VE	11	8	1	4	1	0

Note: Frequently a case had more than one adverse pregnancy outcome, so it had been taken into account for more than one time; def: deficiency.

We observed more than two thrombophilia markers were positive in 41.9% and more than three markers were positive in 6.5% of the thromphophilia cases. We also found that 100% of cases with ≥ 3 markers positive had 2 or more manifestations of adverse pregnancy outcome whereas only 43.7% cases with single marker positive had 2 or more complications (Table 6).

In cases with history of abortion, prevalence of ACLA and protein C deficiency were 23.07%. LA and protein S deficiency was present in 15.38% and 19.23% respectively (Table 4). We found statistically significant association with ACLA, protein-S deficiency, and protein-C deficiency. The most significant association of abortion and thrombophilia was observed between

protein S deficiency and ACLA (p value = 0.02, odds ratio = 32.02 95% C.I=1.72 to 594.92).Among the acquired thrombophilias, Vora found significant association with LA too (p value = 0.01).[1] However in our study we did not found any statistically significant association between LA and abortion .

In our study, cases with pregnancy induced hypertension had LA and ACLA and protein-C positive in 29.4% cases, Protein S was deficient 20.6% cases. Excess of factor VIII and fibrinogen was present in 14.7% and 8.8% cases (Table 4).

Table 5: Significance of presence of thrombophilia markers with various pregnancy outcome.

	Factors	Abortion	PIH	IUD	IUGR	Abruption	DVT
	LA +	8.9091	20.4167	24.5	13.3636	32.6667	98
95 % CI:		0.9406 to 84.3866	2.4682 to 168.8859	2.1856 to 274.6363	1.2671 to 140.9397	2.2654 to 471.0376	4.3637 to 2200.9029
z statistic		1.907	2.798	2.594	2.157	2.561	2.888
Significance level		P = 0.0566	P = 0.0051	P = 0.0095	P = 0.0310	P = 0.0104	P = 0.0039
Odds ratio	ACLA +	32.0244	43.2857	17.8235	43.2857	9.1818	168.3333
95 % CI:		1.7239 to 594.9212	2.4351 to 769.4364	0.6693 to 474.6778	2.1627 to 866.3524	0.1652 to 510.2009	5.3793 to 5267.6648
z statistic		2.325	2.566	1.72	2.465	1.082	2.918
Significance level		P = 0.0201	P = 0.0103	P = 0.0854	P = 0.0137	P = 0.2794	P = 0.0035
Odds ratio	P-C def +	9.8	20.4167	24.5	13.3636	12.25	98
95 % CI:		1.0854 to 88.4850	2.4682 to 168.8859	2.1856 to 274.6363	1.2671 to 140.9397	0.6390 to 234.8223	4.3637 to 2200.9029
z statistic		2.033	2.798	2.594	2.157	1.663	2.888
Significance level		P = 0.0421	P = 0.0051	P = 0.0095	P = 0.0310	P = 0.0963	P = 0.0039
Odds ratio	P-S def +	32.0244	27.5455	17.8235	30.7391	72.1429	60.6
95 % CI:		1.7239 to 594.9212	1.5153 to 500.7169	0.6693 to 474.6778	1.4827 to 637.2678	2.8713 to 1812.6501	1.9365 to 1896.3593
z statistic		2.325	2.241	1.72	2.215	2.601	2.336
Significance level		P = 0.0201	P = 0.0250	P = 0.0854	P = 0.0268	P = 0.0093	P = 0.0195
Odds ratio	FVIII excess	10.3061	18.8305	5.3158	43.2857	33.6667	60.6
95 % CI:		0.4763 to 223.0206	1.0050 to 352.8355	0.0992 to 284.7159	2.1627 to 866.3524	1.1898 to 952.6672	1.9365 to 1896.3593
z statistic		1.487	1.963	0.823	2.465	2.062	2.336
Significance level		P = 0.1370	P = 0.0496	P = 0.4107	P = 0.0137	P = 0.0392	P = 0.0195
Odds ratio	FIBRINOGEN excess	1.96	4.7419	1.7368	13.3636	12.25	4.7143
95 % CI:		0.1176 to 32.6666	0.4719 to 47.6520	0.0657 to 45.9321	1.2671 to 140.9397	0.6390 to 234.8223	0.1606 to 138.3614
z statistic		0.469	1.322	0.33	2.157	1.663	0.899
Significance level		P = 0.6392	P = 0.1861	P = 0.7411	P = 0.0310	P = 0.0963	P = 0.3685

Statistically significant association was found between LA, ACLA and protein C deficiency with PIH, p value were 0.0051, 0.0103 and 0.0051 respectively and Odd ratios were 20.4; 43.28 and 20.4 respectively (Table 5). This finding corroborating with Robertson and other systemic review.[7] Yasuda et al found a relative risk of 6.2 (2.43 - 16.0) in cases with PIH and ACLA.[12] Among the cases presented with intrauterine fetal death LA and protein C deficiency was present 33.3% cases respectively, ACLA and protein S deficiency present in 11.1%. (Table 6). Our study had significant p value of LA and protein C with IUD (i.e.0.0095) (Table 5). The cases with intrauterine fetal growth restriction in our study had significant association with all the factors studied. Highest with F-VIII excess, ACLA had pvalue: 0.0137. LA and protein C deficiency and fibrinogen excess had p value of 0.0310, (Table 5). P-S deficiency had P value 0.00268. In our study, among the 5 cases of abruption, 4 cases (80%) were positive for thrombophilia, 2 was positive for LA and protein S deficiency (Table 4). Though case with abruption had higher prevalence of thrombophilia positive versus negative cases (80% versus 20%) but any significant association was yet to be concluded due to small number of cases.

Table 6: Distribution of thrombophilia positive cases according to the presence of single/multiple thrombophilia markers and their significance.

	Case	Percentage	Single Complication	Percentage	2 Complication	Percentage	≥3 Complication	Percentage
single marker	16	45.7	9	56.3	5	31.2	2	12.5
2 markers	13	37.1	6	46.2	7	53.85	0	
≥3 markers	6	17.2	0	0	3	50	3	50

Table 7: Incidence of 1st and 2nd trimester abortion in thrombophilia positive and thrombophilia negative patients.

Markers	Early abortion	Late abortion	%	Control
LA +	2	2	15.38	1
ACLA +	1	5	23.07	0
P-C DEF +	0	5	19.23	1
P-S DEF +	1	5	23.07	0
F-VIII excess	0	2	7.69	0
Fibrinogen excess	0	1	3.84	1
THR+VE	3	12	57.69	3
THR -VE	7	4	42.31	47

Table 8: Significance of presence of thrombophilia markers with early and late miscarriage.

Markers	Analysis	Early abortion	Late abortion
LA +	Odds ratio	12.25	7
	95 % CI:	0.9914 to 151.3637	0.5904 to 82.9969
	z statistic	1.953	1.542
	Significance level	P = 0.0508	P = 0.1230
ACLA +	Odds ratio	15.9474	48.3043
	95 % CI:	0.6032 to 421.6414	2.4904 to 936.9387
	z statistic	1.657	2.563
	Significance level	P = 0.0974	P = 0.0104
P-C DEF +	Odds ratio	1.5714	22.2727
	95 % CI:	0.0598 to 41.3138	2.3606 to 210.1482
	z statistic	0.271	2.71
	Significance level	P = 0.7864	P = 0.0067
P-S DEF +	Odds ratio	15.9474	48.3043
	95 % CI:	0.6032 to 421.6414	2.4904 to 936.9387
	z statistic	1.657	2.563
	Significance level	P = 0.0974	P = 0.0104
F-VIII excess	Odds ratio	4.8095	17.4138
	95 % CI:	0.0902 to 256.3563	0.7907 to 383.4944
	z statistic	0.774	1.811
	Significance level	P = 0.4388	P = 0.0701
FIBRINOGEN excess	Odds ratio	1.5714	3.2667
	95 % CI:	0.0598 to 41.3138	0.1925 to 55.4413
	z statistic	0.271	0.819
	Significance level	P = 0.7864	P = 0.4126
THR+VE	Odds ratio	6.7143	47
THR -VE	95 % CI:	1.1249 to 40.0746	9.2487 to 238.8457
	z statistic	2.089	4.642
	Significance level	P = 0.0367	P < 0.0001

Among 3 cases complicated with deep vein thrombosis, LA, ACLA, protein C deficiencies were present in 2 cases (Table 4). Deep vein thrombosis was significantly associated with LA, ACLA, P-C def, P-S def, F-VIII excess (p value= 0.0039, 0.0035, 0.0039, 0.0195, and 0.0195 resp.) (Table 5). But any conclusion cannot be drawn due to small prevalence of study group in the study group.

50% of abortions associated with LA were in 1st trimester abortions which was highest among all other thrombophilia associated 1st trimester abortions.But p value (0.0508) was not significant.

We observed, ACLA, protein C and protein S deficiency were significantly associated with 2nd trimester abortions, with p value 0. 0.0104, 0.0067, 0.0104 and OR of 48.3043, 22.2727and 48.3043 respectively.

When presence of thrombophilia was taken into consideration in our study, it was strongly associated with 2nd trimester abortions (p value = <0.0001, OR = 47, C.I. = 9.2487 to 238.8457) (Table 8).

DISCUSSION

This study shows high prevalence of thrombophilia in eastern part of Uttar Pradesh, India, who had history of adverse pregnancy outcome showing thrombophilia was ten times more prevalent (64.8%) in cases with adverse pregnancy outcomes than in general population. Vora et al found 75.6% of unexplained fetal loss had either an acquired, genetic or both marker's of thrombophilia present.[1] Koeleman reported FV leiden mutation was associated with potein S decicient probands (38%), and activated protein c resistance among symptomatic protein-C probands.[8] This suggested high probability of presence of more than one thrombophilia in more severe cases. We found that there was increased severity of adverse pregnancy outcome when there was presence of combined defect or more than 1 thrombophilia markers positive. Prevalence of different thrombophilia markers are studied in individual case and association to various adverse outcomes were noted in this study. Significant association was observed between LA and all manifestations of adverse pregnancy outcome. Cecile M Yelnik in an analysis of PROMISSE study supported association of LA with adverse pregnacy outcome more than ACLA/ β2glycoprotein1.[15] We had strongest association of Protein S deficiency and abruption in our population than any other association. De vries also found 29% of abruption cases had Protein S deficiency.[16]

But Alfirevinc Z, in his systemic review concluded association of ACLA and APC-R with abruption is strongest.[10] It is correctly stated by Alfirevic Z that there is wide heterogenicity in the prevalence of thrombophilia between different studies, but that is probably due to cases were selected from several different races worldwide. As treatment was found significantly effective in literature, screening of these markers should be done in patients with bad obstetric history.

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