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Original Research Article

Efficacy of anti-thrombotic treatment in thrombophilia patients with adverse pregnancy outcome

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ABSTRACT

Background: Thrombophilia is a potentially treatable cause of adverse pregnancy outcome. The objective was to compare the fetomaternal outcome in thrombophilia patients with adverse pregnancy outcome after treating with low-molecular-weight (LMW)/ unfractionated heparin and aspirin.
Methods: 54 antenatal women studied who had an earlier or presenting pregnancy complicated by adverse pregnancy outcome were included in this study. In the present pregnancy, therapy consisting of LMW heparin and aspirin was administered who were found to be thrombophilia positive. Patients also received folic acid supplementation throughout their pregnancy. The fetomaternal outcome is compared according to the time of initiation of treatment.
Results: Low-molecular-weight heparin and aspirin was well tolerated and none of the women or the newborns developed any hemorrhagic complications.3 thrombophilia negative cases with history of recurrent pregnancy loss aborted even getting treatment from 1 trimester. 1 thrombophilia positive case with history of recurrent pregnancy loss aborted when received treatment from 2nd trimester. There is 25.8% increase in birth weight of neonate if thrombophilia positive cases were treated from 1st trimester. Whereas there was only 10.23% increase in birth weight in thrombophilia negative cases when treated from first trimester. We found, our treatment was significantly effective in preventing IUD, IUGR, abruption, abortion, eclampsia. Though prevention of PIH had no significant correlation with antithrombotic treatment, only 2 cases booked from 1st trimester developed PIH among thrombophilia positive cases. But neither of cases had suffered from any severe complication as compared to 81% of eclampsia cases, 16.67% of DVT cases, 1 case of mortality in cases treated after third trimester.
Conclusions: This case control trial suggests that patients with adverse pregnancy outcome and thrombophilia may get benefit from treatment with combined LMW heparin and aspirin in subsequent pregnancies. We suggest all patients with adverse pregnancy outcome should be investigated for thrombophilia markers.

Keywords: Adverse pregnancy outcome, Anti-thrombotic treatment, Aspirin, LMW heparin, Thrombophilia, Unfractionated heparin

INTRODUCTION

Thrombophilia is a potentially treatable cause of adverse pregnancy outcome. The purpose of anticoagulation is to reduce the risk of placental thrombosis and to improve the outcome of pregnancy. It is rather difficult to establish the guidelines for antithrombotic therapy in pregnancy due to the lack of relevant and well-controlled trials. Moreover, the recommendations regarding prophylactic and therapeutic strategies in pregnancy are largely based on clinical trials in non-pregnant populations.[1]

The currently available antithrombotics for prevention and treatment include heparin (low molecular weight heparin or unfractionated heparin), aspirin and coumarin derivatives. Based on safety data, a heparin-related compound (LMWH or UFH) and aspirin are the anticoagulant of choice during pregnancy in which its efficacy is established.[2,3]

Several studies are available comparing low dose aspirin and heparin but results are controversial. Farquharson et al found high success rate is achieved when low-dose aspirin is used for antiphospholipid syndrome in pregnancy.[4] The addition of low molecular weight heparin does not significantly improve pregnancy outcome. Gris et al found better outcome with enoxaparin (69 live birth /80) compared with aspirin alone (23 live birth/ 80) in case of inherited thrombophilia.[5] Paidas et al found that women who received prenatal heparin therapy had a nearly 80% reduction in the risk of overall adverse pregnancy outcome compared to untreated controls.[6] In a systemic review, Duley et al demonstrated that use of antiplatelet agents, mostly low-dose aspirin, is associated with a 15% reduction in the risk of preeclampsia and 14% in the risk of fetal or neonatal death.[7] Similar result has cited by Line Leduc et al 20% and 30% reduction in the respective risk of preeclampsia and fetal growth restriction with the use of low-dose ASA.[8] Leduc, has found that 90% had a normal outcome who have received prophylaxis while 75% had adverse outcome who have not received prophylaxis in pregnancy.

Because the risk of a primary venous thromboembolic event is less than 1% for most thrombophilic women, routine anticoagulant therapy does not seem prudent for this indication. Given the low absolute risk of venous thromboembolism, the cost and potential side effects of anticoagulant use are difficult to justify.

Since anticoagulants for primary prevention of adverse pregnancy outcomes in thrombophilic women have not yet been shown to have a definitive benefit, they are not yet recommended for this purpose.

Prophylactic anticoagulation during pregnancy can be with either LMWH or unfractionated heparin. Thromboprophylaxis with LMWH can be with lower, fixed, once-daily doses throughout pregnancy, although some clinicians still prefer twice-daily dosing.[9] Few studies support heparin to be started as soon as pregnancy is confirmed. Brenner, Farquharson continued throughout pregnancy.[10,4] ACOG supports the recommendation to consider the use of low-dose aspirin (81 mg/day), initiated between 12 and 28 weeks of gestation.[11,12] While Kupferminc started LMWH from 5-15 weeks to 38 weeks/till upto delivery in RPL in patients without thrombophilia.[13] Kaandorp randomly assigned to receive aspirin combined with low-molecular-weight heparin (combination-therapy group), aspirin alone, or placebo either before conception or at a gestational age of less than 6 weeks in RPL patients with thrombophilia.[14] Rai started low dose aspirin (75 mg daily) or low dose LMW heparin when they had a positive urine pregnancy test.[15] Women were randomly allocated aspirin or heparin when fetal heart activity was seen on ultrasonography in this study. The FRUIT RCT found that adding LMWH to aspirin before 12 weeks gestation reduced the risk of recurrent early onset pre-eclampsia in women with inherited thrombophilia and prior delivery for pre-eclampsia/fetal growth restriction before 34 weeks.[16]

Heparin therapy must be interrupted temporarily during the immediate peripartum interval to minimize the risk of hemorrhage and to allow for the option of regional anesthesia. As mentioned earlier, because of the theoretical risk of paraspinal hemorrhage in women receiving heparin who undergo epidural or spinal anesthesia, the American Society of Regional Anesthesia guidelines advise waiting to insert the needle at least 10 to 12 hours after the last prophylactic dose of LMWH, and at least 24 hours after the last therapeutic dose.[17]

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, India. 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. Pearson correlation coefficient is used to find out the efficacy of treatment.

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 or previous history of recurrent miscarriage. Previous miscarriage was defined as pregnancy loss at a gestational age of 20 weeks or less. The definition of miscarriage included

documentation of pregnancy by a positive pregnancy test and clinical manifestations of miscarriage (e.g., abdominal pain, cramps, and vaginal bleeding); it did not include the loss of a biochemical pregnancy. Recurrent miscarriage was defined as at least two miscarriages.

Study group was subjected to following protocol

- Detail history and clinical examination.
- Investigations

Routine blood and urine investigation

Tests to rule out other causes of adverse pregnancy outcomes

Screening coagulation test- PT, APTT, factor VII assay, fibrinogen

Test for thrombophilia markers

Participating women were tested once for plasma activity levels of protein C, protein S, lupus anticoagulant, IgG and IgM anticardiolipin antibodies, D-dimer, Factor VIII excess and Fibrinogen excess. Deficiencies were defined as less than 70% of normal activity for protein C, less than 35% of normal activity for total protein S.

All the cases found to have thrombophilia marker positive are subjected to low molecular weight/unfractionated heparin and low dose aspirin 75mg/day if registered within 28 weeks. All patients were given 5 mg folic acid /day throughout the pregnancy. The fetomaternal outcome is compared according to the time of initiation of treatment.

RESULTS

In present study, we observed that there were significant risks of recurrence of adverse pregnancy outcome in subsequent pregnancy where there were histories of IUD and DVT in thrombophilia positive cases. There was higher history of RPL (57.6% vs 42.3%), PIH (63.6% vs. 36.3%), IUGR (64.8% vs 35.2%) and Abruption (80% vs 20%) in thrombophilia cases compared with that of thrombophilia negative cases. (Table 1a) with maximum odd's ratio in cases with history of IUD (OR: 66.58) and abruption (OR: 62.66) (Table 1b).

In present study 31.48% cases were booked from 1st trimester (group 1) 20.37% cases were booked from 2nd trimester (group 2) only 14.82% cases were treated from 3rd trimester (group 3) and 33.33% cases where unbooked/not received any treatment except hematinic supplementation (group 4) (Table 2).

In case of RPL cases, 3 (3/19) thrombophilia marker negative cases aborted inspite of getting treatment from 1st trimester but no single thrombophilia positive case aborted when booked from 1st trimester. 1 case expelled prematurely around 18 weeks of gestational age when treated from second trimester (Table 3). There is 25.8% increase in birth weight of neonate if the thrombophilia positive cases were treated from 1st trimester in comparison with group 4.

Table 1a: Incidence of previous history of adverse pregnancy outcomes in thrombophilia positive and thrombophilia negative patients.

	THR +ve	THR -ve
RPL	15	11
PIH	7	4
IUD	17	4
IUGR	11	6
Abruption	4	1
DVT	1	0
Control	3	47

Note: The above table shows the risk of recurrence of adverse pregnancy outcome in study group presenting with adverse pregnancy outcome in this pregnancy. Frequently a case had history of more than one adverse pregnancy outcome so some of the cases have been taken into account for more than one time.

Table 1b: Risk of adverse pregnancy outcome in thrombophilia cases with previous positive history.

	Thrombophilia	
RPL	Odds ratio	21.3636
	95 % CI:	5.2539 to 86.8694
	z statistic	4.278
	Significance level	P<0.0001
PIH	Odds ratio	27.4167
	95 % CI:	5.0360 to 149.2604
	z statistic	3.83
	Significance level	P=0.0001
IUD	Odds ratio	66.5833
	95 % CI:	13.4908 to 328.6200
	z statistic	5.155
	Significance level	P<0.0001
IUGR	Odds ratio	28.7222
	95 % CI:	6.1974 to 133.1159
	z statistic	4.291
	Significance level	P<0.0001
Abruption	Odds ratio	62.6667
	95 % CI:	5.2333 to 750.4135
	z statistic	3.267
	Significance level	P=0.0011
DVT	Odds ratio	40.7143
	95 % CI:	1.3866 to 1195.5168
	z statistic	2.15
	Significance level	P=0.0316

Whereas, there was only 10.23% increase in birth weight in thrombophilia negative cases when treated from first trimester in comparison with group 4 (Table 4).

Table 2: Distribution of cases according to their duration of treatment.

	1st trimester	2nd trimester	3rd trimester	unbooked
THR +ve	8	8	6	14
THR -ve	9	3	2	4
Total	17	11	8	18

Table 3: Incidence of abortion in thrombophilia positive and thrombophilia negative cases after receiving treatment.

	THR +ve	THR -ve
1st trimester	0	3
2nd trimester	1	0
3rd trimester	0	0
Unbooked	NA	NA

These results showed that thrombophilia is a potentially treatable entity and early treatment is associated with better outcome. We found, our treatment was significantly effective in preventing IUD, IUGR, abruption, abortion, eclampsia. Though prevention of PIH had no significant correlation with antithrombotic treatment, Only 33.33% case booked from 1st trimester developed PIH in thrombophilia positive cases in comparison of 92.86% unbooked PIH cases. But neither of cases had suffered from any severe complication as compared to 81% of eclampsia cases, 16.67% of DVT cases, 1 case of mortality in cases from group 3 and group 4 (Table 5).

Table 4: Mean baby weight after receiving treatment in thrombophilia positive and negative cases.

	Mean baby weight (kg)	
	THR+ve	**THR -ve**
1st trimester	2.73	2.8
2nd trimester	2.35	2.65
3rd trimester	2.17	0
Unbooked	2.17	2.54

Table 5: Efficacy of anti-thrombotic treatment in thrombophilia patients in prevention of adverse pregnancy outcome.

	1st trimester	2nd trimester	3rd trimester	Unbooked	Pearson correlation coefficient (r)
PIH	2	5	6	13	-1
No PIH	6	3	0	1	
IUD	0	0	0	8	+1
No IUD	8	8	6	6	
IUGR	0	1	5	4	+1
No IUGR	8	7	1	10	
Abruption	0	1	0	4	+1
No abruption	8	7	6	10	
Abortion	0	1	NA	NA	+1
No abortion	8	7	NA	NA	
DVT	0	0	0	2	+1
No DVT	8	8	6	12	
Eclampsia	0	0	1	8	+1
No Eclampsia	8	8	5	6	
Mortality	0	0	0	1	+1
No Mortality	8	8	6	13	

DISCUSSION

There are several studies which evaluated risk factors for these adverse pregnancy outcomes. A prior history of any of these pregnancy complications is the strong predictor of the occurrence of any of this complication in subsequent pregnancy. Carp treated 37 patients with daily subcutaneous injections of enoxaparin 40 mg and 48 were not treated.[18] Twenty-six of the 37 pregnancies in treated patients (70.2%) resulted in live births, compared with 21 of 48 (43.8%) in untreated patients (P<0.02, OR 3.03, 95% CI 1.12-8.36). The beneficial effect was seen mainly in primary aborters, i.e. women with no previous live births (P<0.008, OR 9.75, 95% CI 1.59-52.48). Brenner treated sixty-one pregnancies with the low molecular weight heparin enoxaparin throughout gestation until 4 weeks after delivery following diagnosis of thrombophilia.[10] Dosage was 40 mg/day in women with

solitary defect and 80 mg/day in combined defects. Aspirin, 75 mg daily was given in addition to enoxaparin to women with antiphospholipid syndrome. They concluded enoxaparin is safe and effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia. Brenner et al had found in his live-enox study, a multicentre prospective randomized trial, statistically significant improved outcome, in live birth rate, preeclampsia, and abruption after treatment.[19] The p values were <0.01 for each. Kupferminc et al had similar findings.[20] Their treated patients had babies with higher birth weight. Riyazi et al found similar result.[21] Kaandorp measured live birth rate which did not differ significantly.[14] In addition, the live birth rate in the placebo group of 67% was higher than that in the aspirin only group (61.6%), giving a non-significant absolute risk difference of 5.4% (95% CI- 18.6-7.8). Gris et al had odds ratio 15.5 and p value <0.0001 in successful treatment in pregnancy complicated with thrombophilia.[5]

CONCLUSION

Thrombophilic conditions are associated with a spectrum of pregnancy complication. There was high prevalence of thrombophilia in present study group. Treatment was also proved to be effective and significant correlation value except in mild/moderate PIH. There was higher increase in birth weight in newborns with thrombophila positive mothers than thrombophilia negative mothers suggesting thrombophilia holds better prognosis than unexplained/ other pathology when treated early. But there is lack of adequate size, randomized, placebo controlled trial for prevalence and significance of association of thrombophilia and adverse pregnancy outcome in Indian population. Further studies should be conducted and proper guidelines should be postulated to avoid thrombophilia complications and better feto-maternal outcome.

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REFERENCES

1. Kupferminc MJ. Thrombophilia and pregnancy. Reprod Biol Endocrinol. 2003;1:11.
2. Bates SM, Ginsberg JS. How we manage venous thromboembolism during pregnancy. Blood. 2002;100(10):3470-8.
3. Bates S, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy. Chest. 2004;126:627S-44S.
4. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. Obstet Gynecol. 2002;100: 408-13.
5. Gris JC, Mercier E, Quéré I, Lavigne-Lissalde G, Cochery-Novellon E, Hoffet M, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. Blood. 2004;103:3695-9.
6. Paidas M, Ku DH, Triche E, Lockwood C, Arkel Y. Does heparin therapy improve pregnancy outcome in patients with thrombophilia? J Thromb Haemost. 2004;2:1194-5.
7. Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. BMJ. 2001;322(7282):329-33.
8. Leduc L, Dubois E, Takser L, Rey E, David M, Dalteparin and low-dose aspirin in the prevention of adverse obstetric outcomes in women with inherited thrombophilia. J Obstet Gynecol Can. 2007;29(10):787-93.
9. Ellison J, Walker ID, Greer IA. Antenatal use of enoxaparin for prevention and treatment of thromboembolism in pregnancy. BJOG. 2000;107:1116-21.
10. Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost. 2000;83: 693-7.
11. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive services task force. Ann Intern Med. 2014;160:695-703.
12. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive services task force recommendation statement. U.S. Preventive services task force. Ann Intern Med. 2014;161:819-26.
13. Michael K, Eli R, Ariel M, Sharon M, Lessing JB, Gamzu R. Low molecular weight heparin versus no treatment in women with previous severe pregnancy complications and placental findings without thrombophilia. Blood Coagulation and Fibrinolysis. 2011;22(2):123-6.
14. Kaandorp SP, Goddijn M, van der Post JAM, Hutten BA, Verhoeve HR, Hamulyák K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med. 2010;362:1586-96
15. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ. 1997;314(7076):253-7.
16. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH; FRUIT investigators. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. J Thromb Haemost. 2012;10(1):64-72.
17. Horlocker TS, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or

thrombolytic therapy: American society of regional anesthesia and pain medicine evidence-based guidelines (third edition). Regional Anesthesia and Pain Medicine. 2010;35(1):64-101.
18. Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. J Thromb Haemost. 2003;1:433-8.
19. Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J; LIVE-ENOX investigators. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. J Thromb Haemost. 2005;3:227-9.
20. Kupferminc MJ, Fait G, Many A, Lessing JB, Yair D, Bar-Am A, et al. Low-molecular-weight heparin for the prevention of obstetric complications in women with thrombophilias. Hypertens Pregnancy. 2001;20:35-44.
21. Riyazi N, Leeda M, de Vries JI, Huijgens PC, van Geijn HP, Dekker GA. Low-molecular-weight heparin combined with aspirin in pregnant women with thrombophilia and a history of preeclampsia or fetal growth restriction: a preliminary study. Eur J Obstet Gynecol Reprod Biol. 1998;80:49-54.

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