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Thrombophilia, Anticoagulant Therapy, and Pregnancy Outcome in Women with Poor Obstetric History

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ABSTRACT

Background: The role of anticoagulant medications in preventing placental mediated pregnancy complications in patients with and without thrombophilia has not been investigated well. One underlying cause is associated with adverse effects of anticoagulants in pregnancy including teratogenicity, complexities in dosing and management of anticoagulants during pregnancy and labor. We aimed to assess effects of prophylactic anticoagulant medications in pregnant women with history of the PMPCs who were tested for hereditary thrombophilia.
Methods: This retrospective cohort study was done in obstetric clinics of Tehran University of Medical Sciences on medical records of 148 pregnant women with history of poor obstetric outcome due to placental complications. Pregnant women with both positive and negative thrombophilia test results were included in the study. They were divided into two group according to receiving anticoagulants.
Results: 148 patients were analyzed over 1.5 years. Among them, 85 women received anticoagulant medications and 63 did not receive these treatments for the next pregnancy. Moreover, 58 out of 148 pregnant women were thrombophilic according to positive tests. Successful pregnancy outcomes were significantly higher in treated groups. The risk of abortion and unsuccessful pregnancy was significantly reduced in the treated groups. The occurrence of intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), and preeclampsia were not reduced. The use of anticoagulant during pregnancy did not have any adverse effects. The results in thrombophilia group and non-thrombophilia group demonstrated the benefit of anticoagulant therapy in improvement of pregnancy outcomes.
Conclusion: Testing for inherited thrombophilia in women who have experienced placental mediated pregnancy complications is not recommended. Anticoagulant therapy can be useful in women without thrombophilia and with poor obstetric history because of placental mediated pregnancy complications.

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Introduction

Placental mediated pregnancy complications (PMPCs) are defined as several maternal or fetal complications during pregnancy that may be associated with placental insufficiency. The PMPCs include early and late pregnancy loss, placental abruption, fetal growth restriction and preeclampsia.[1] These complications are common and significantly increase maternal and fetal morbidity and mortality.[1]

Women with history of the PMPCs may develop similar complications in following pregnancies. As a result, primary and secondary preventive strategies are required

to avoid complicated pregnancies in women with a history of PMPCs.[2]

According to the literature, several studies have provided contradicting results about effects of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) on pregnancy outcomes in women with poor obstetric history.[3-5]

One potential underlying cause of the PMPC is thrombotic events in placental vessels.[6-9] That is why anticoagulant medications (e.g. UFH and LMWH) can prevent these complications through inhibiting complement system, reducing vascular resistance, and modulating trophoblastic invasion.[10]

In contrast to positive impact of anticoagulants on PMPCs, UFH and LMWH may adversely affect the fetus and threaten pregnant women with bleeding events.[11-13]

One of the major indications for using anticoagulants during pregnancy is positive tests for hereditary thrombophilia that assess hereditary states causing thromboembolism including protein C, S and antithrombin deficiency, factor V Leiden, hyperhomocysteinemia and mutation in the gene encoding prothrombin G20210. Hereditary thrombophilia can be associated with venous thrombotic events which is supposed to be managed by anticoagulant medications. Many physicians screen pregnant women for hereditary thrombophilia and prescribe anticoagulants after developing any PMPC event.[14, 15] However, advantages and disadvantages of conducting hereditary thrombophilia tests and prophylactic therapy with anticoagulants have not studied well in women with history of the PMPCs.[9, 16, 17]

In the current study, we aimed to assess effects of prophylactic anticoagulant medications in pregnant women with history of the PMPCs who were tested for hereditary thrombophilia.

Materials and Methods

This retrospective cohort study was done in obstetric clinics of Tehran University of Medical Sciences. 148 pregnant women were enrolled into the study with at least one of the following complications in their previous pregnancies: intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), severe preeclampsia, placental abruption, and recurrent abortion. The IUFD was defined as fetal death after 20th week of gestation. IUGR was characterized as birth weight below the 10th percentile of gestational age and recurrent abortion was considered as three or more miscarriages before 20th weeks during previous pregnancies. Moreover, participants with history of documented thrombotic disease (e.g. deep vein thromboembolism), diabetes mellitus, thyroid disorders, autoimmune disorders, documented antiphospholipid syndrome, assisted fertility (e.g. in vitro fertilization) and abnormal fetal or parental karyotypes were excluded from the study due to their possible influence on the pregnancy outcome.[14]

All participants were tested for hereditary thrombophilia before their recent pregnancy consisting of protein C, protein S, homocysteine and antithrombin levels, activated protein C resistance and factor V Leiden mutation, and prothrombin G20210 gene mutation.

The participants were categorized based on their test results into two groups of positive and negative for thrombophilia. Each group was classified into two subgroups in regards to receiving anticoagulant therapy in their last pregnancy. The anticoagulation in the treated group consisted of low molecular weight heparin or unfractionated heparin plus acetylsalicylic acid 80 mg/day by the end of their pregnancy regardless of being thrombophilia positive or negative. The primary endpoints were pregnancy outcome and occurrence of PMPCs.

Analysis of variance (ANOVA) was used to assess the differences between the two groups of the study, and Chi-square tests were applied to determine the association between the categorical variables. The analyses were performed using SPSS software, version 26.

Results

Between September 2018 and February 2020, 148 participants were enrolled into the study, among whom 58 were positive for thrombophilia. In the thrombophilia positive group, 30 women received anticoagulant medications and ASA, while 28 cases did not receive any medications. In the thrombophilia negative group, 55 pregnant women underwent anticoagulant therapy and ASA. Among those with negative test for thrombophilia, 35 women did not receive anticoagulants and ASA. The participants with a positive thrombophilia test who received anticoagulation therapy had an age range of 32.33±4 years with gravidity of 3.5±1, parity of 1.07±0.6, mean number of abortions of 1.47±1, and mean number of live births of 0.33±0.3. In this group, 6 out of 30 participants (20%) had history of severe preeclampsia, 9 (30%) individuals had recurrent abortion, 10 (33%) had IUFD, only 1 participant from this group had placental abruption and 4 (13.3%) individuals had history of IUGR.

Participants with ax positive thrombophilia test who did not receive anticoagulation had an age range of 31.1±4 years with gravidity of 3.14±1, parity of 1.11±0.6, mean number of abortions of 1.11±1, and mean number of live births of 0.46±0.4. In this group, 2 out of 28 participants (7.1%) had history of severe preeclampsia, 9 (32.1%) had recurrent abortions, 15 (53.5%) had IUFD, only 1 participant had placental abruption and 1 (3.6 %) had history of IUGR. There were no significant differences in demographic characteristics of this group (Tables 1 and 2).

Patients with thrombophilia negative tests who were treated with anticoagulants had a mean age of 32.93±4 years with gravidity of 3.81±1and parity of 1.37±0.8. Their mean number of abortions was 1.57±1, mean number of live birth was 0.56±0.5. In previous pregnancies, 8 out of 55 participants (14.5%) had severe preeclampsia,18 (32.7%) had experienced recurrent abortions, 22 (40%) had IUFD, 4 (7.2 %) had placental abruption and 4 (7.2 %) from this group had history of IUGR. Participants with thrombophilia negative test who did not receive anticoagulant during pregnancy had a mean age of 32.83±4 years with gravidity of 3.49±1, parity of 1.2±0.8, and number of abortions of1.3±1. Their mean number of

Table 1: Participants' gestational history in treatment and non-treatment groups in thrombophilia positive and negative groups.

Participants' gestational history	Thrombophilia positive/ treated (total N=30)	Thrombophilia negative/treated (N=55)	Thrombophilia positive/non-treated (N=28)	Thrombophilia negative/non-treated (N=35)	P value
Age (years)	32.33±4	32.93±4	31.15±4	32.83±4	0.4
Average Number of previous gravidity	3.5±1	3.81±1	3.14±1	3.28±1	0.116
Average Number of previous Parity	1.07±0.6	1.37±0.8	1.11±0.6	1.11±1	0.26
Average Number of previous Abortions	1.47±1	1.57±1	1.11±1	1.25±1	0.6
Average Number of previous Live child	0.33±0.3	0.56±0.5	0.46±0.4	0.44±0.4	0.36

Table 2: Participants' PMPCs history in treatment and non-treatment groups in thrombophilia positive and negative groups.

Participants' previous PMPCs history	Thrombophilia positive/treated group (total N=30)	Thrombophilia negative/treated group (N=55)	Thrombophilia positive/non-treated group (N=28)	Thrombophilia negative/non-treated group (N=35)	P value
Severe preeclampsia	6 (20%)	8 (14.5%)	2 (7.1%)	3(8.5%)	0.6
Recurrent Abortions	9 (30%)	18 (32.7%)	9 (32.1%)	10 (28.5.4%)	0.9
IUFD	10 (33%)	22 (40%)	15 (53.5%)	15 (42.8%)	0.5
Placental abruption	1 (3.3%)	4 (7.2%)	1 (3.6%)	1 (2.8%)	0.7
IUGR	4 (13.3%)	4 (7.2%)	1 (3.6%)	6 (17%)	0.3

Table 3: Frequency of thrombophilia

	Thrombophilia positive group (total=58)	Treated group (N=30)	Non-treated group (N=28)	P value
Protein S deficiency	3 (5.1%)	1 (3.3%)	2 (7%)	0.47
Protein C deficiency	8 (13.7%)	4 (13.3%)	4 (14.2%)	0.33
Hyperhomocysteinemia	21 (36.2%)	10 (33.3%)	11 (39.2%)	0.55
Prothrombin G20210A mutation	0	0	0	-
Anti-thrombin deficiency	4 (6.8%)	2 (6.6%)	2 (7%)	0.4
Factor 5 Leiden/APCR (heterozygote)	17 (29.3)	10 (33.3%)	7 (25%)	0.07
Factor5 Leiden/APCR (homozygote)	5 (8.6%)	3 (10%)	2 (7%)	0.5

Table 4: Pregnancy outcome in treated and non-treated groups

	Pregnancy outcome	Treated	Non-treated	P value	RR (CI95%)
Thrombophilia negative group	Successful without complication	37 (67.2%)	10 (28.5%)	0.001	2.35 (1.35-4.1)
	Total number	54 (100%)	35 (100%)		
Thrombophilia positive group	Successful without complication	16 (53.5%)	3 (10.7%)	0.001	4.9 (1.6-15)
	Total number	30(100%)	28(100%)		

live births was 0.47±0.4. 3 out of the35 participants (8.5%) with severe preeclampsia in their history, 10 (28.5%) individuals had recurrent abortions, 15 (42.8%) had history of IUFD, only 1 (2.8%) had placental abruption and 6 (17 %) individuals had IUGR. There were no statistically significant differences between the groups (Tables 1 and 2).

The most common thrombophilia positive test in both treated and non-treated groups was Hyperhomocysteinemia (36%), followed by the factor V Leiden mutation (29.3%) in heterozygote state (Table 3).

Enoxaparin was the most common anticoagulant medication used with ASA in the treated groups (95%) followed by UFH. The main cause for using UFH instead of LMWH was financial issues. More than 86% of women continued anticoagulant and ASA during pregnancy until delivery time, only 7% had mild bleeding (spotting) which led to the discontinuation of the drug. There were not any severe bleeding complications among treated groups.

Successful pregnancy outcomes without any complications were significantly higher in treated groups in both women who were thrombophilia positive (RR=4.9, P<0.01) and negative (RR=2.35, P<0.01) (Table 4).

The risk of abortion and unsuccessful pregnancy were significantly reduced in the treated groups. The risk of IUFD, IUGR, and preeclampsia were not reduced in both thrombophilia positive and thrombophilia negative groups (Table 5).

Discussion

Hereditary thrombophilia increases the risk of perinatal morbidity and mortality specifically the PMPCs.[18] There are numerous studies evaluating pregnant women with poor history in their previous pregnancies. In a study on 204 pregnant women who had poor obstetric history and positive thrombophilia test. In their study, 145 individuals were treated with anticoagulants during their last pregnancy who demonstrated better perinatal outcomes

Table 5: Fetal-maternal complications in treated and non-treated groups

Groups	Sub-Groups	IUGR	IUFD	Placental abruption	Abortion	Severe preeclampsia	Live birth
Thrombophilia negative group	Treated (N=55)	4 (7.2%)	2 (3.6%)	0	8 (14.5%)	3 (5.4%)	40 (72.7%)
	Non-treated (N=35)	5 (14%)	4 (11%)	0	17 (47%)	0	13 (37%)
	P-value [RR (CI95%)]	NS	NS	-	0.001 [1.61(1.18-2.33)]	NS	0.001 [1.9 (1.2-3.1)]
Thrombophilia positive group	Treated (N=30)	3 (10%)	3 (10%)	1 (3%)	5 (17%)	2 (6%)	19 (63%)
	Non-treated (N=28)	2 (7%)	6 (21.4%)	0	14 (50%)	3 (10.6%)	5 (17%)
	P-value [RR (CI95%)]	NS	NS	-	0.007 [1.66 (1.11-2.49)]	NS	0.001 [3.5 (1.5-8.2)]

in their final weeks of gestation which included reducing the number of abortions and increasing number of live births among those women. However, the rate of stillbirth, IUFD, IUGR and placental abruption did not change by receiving anticoagulant therapies.[14] Our results were consistent with these findings, as anticoagulant therapy had positive effects on the rate of live birth and reducing the number of abortions.

It has also been reported that in participants with history of PMPCs and negative thrombophilia tests, anticoagulant therapy can improve pregnancy outcomes as well. Mastrolia and his colleagues conducted a systemic review of five studies including 403 patients with history of preeclampsia or fetal growth restriction. They found a modest beneficial effect of anticoagulantion in preventing preeclampsia and fetal growth restriction.[2] Our results showed reducing abortions and increasing live births in treated subgroup of participants with negative thrombophilia test (RR=2.35).

The effect of anticoagulation therapy in women with thrombophilia positive test was stronger than those with negative tests (RR=4.9 vs 2.3). Based on the chi-square tests, the pregnancy outcome was significantly better in participants who received anticoagulants comparing to those who did not (RR=3.3, P=0.001). Therefore, it can be concluded that pregnant women with poor obstetric history may benefit from anticoagulant therapy without testing for hereditary thrombophilia.

In a retrospective study, 373 pregnant women positive for thrombophilia testing were categorized into two subgroups, 151 and 222 women without and with prior PMPCs, respectively.[19] They found that predisposition for thrombophilia did not have significant associations with PMPCs. They also revealed that LMWH and ASA could prevent the development of the PMPCs in thrombophilia positive pregnant women with history of PMPCs. These findings were consistent with the guideline of the "American College of Chest Physicians" in 2018 that testing for inherited thrombophilia in women with prior complications during pregnancy is not recommended and the only established recommended test is screening for anti-phospholipid antibodies.[20] It is important to mention that we excluded participants with documented anti-phospholipid syndrome (APS) and none of our participants had APS positive tests.

The relative risk of abortion significantly reduced after anticoagulation therapy (RR=1.6), but the risk of IUGR, IUFD, preeclampsia and placental abruption did not significantly decrease. Although the severity of these complications had been reduced, the frequency of live birth was improved significantly in both thrombophilia negative (RR=1.9, P=0.001) and positive groups (RR=3.5). These results were similar to the findings of Mutlu et al. that the abortion rate decreased significantly after anticoagulation therapy.[14] Haddad and his colleagues also showed no positive effects of anticoagulation on reducing the occurrence of preeclampsia.[21] In a systemic review of six randomized controlled trials including a total of 848 pregnant women with prior PMPCs, reduction in all PMPCs (not only recurrent abortions) was observed in individuals who were treated with LMWHs.[22] Therefore, further research is required to assess the effect of anticoagulants on different kinds of PMPCs.

In our study, aspirin had been prescribed along with anticoagulants in all patients in the treated group; hence its effect could not be analyzed. It has been reported that women who received LMWH along with ASA had significantly fewer perinatal complications than those who were only treated with ASA. There was no significant difference in pregnancy outcome between women who were treated with ASA and those who did not receive any treatments.[14] On the other hand, in a systemic review by Arei and her colleagues, there was no significant difference in pregnancy outcome between the group receiving LMWH and ASA with those taking ASA alone.[23]

In the current study, only 7% of women in both thrombophilia positive and negative groups had mild bleeding (spotting) and severe complications of anticoagulation therapy including significant maternal bleeding during pregnancy. In the meantime, no fetus abnormality was found in this study. In accordance with our study, using enoxaparin during pregnancy was associated with a low risk of bleeding risk.[24]

The design of our study was a retrospective one that could have limitations and biases of such studies due to using medical records. Some participants were excluded due to incomplete medical documents. Moreover, it might be suggested that women in the treated group were more compliant to the medical care which could impose confounding effects in the results.

Therefore, longitudinal prospective studies are required to reach a more definite conclusion regarding the benefits of anticoagulation therapy in pregnant women. Direct oral anticoagulants (DOACs) are prescribed more frequently in recent years and are replaced parental anticoagulants in many clinical conditions such as deep vein thrombosis. The safety and efficacy of DOACs during pregnancy in clinical trials is not well studied and their effects on pregnant women and their fetus are not clear. Further investigation in application of DOACs may affect the future of anticoagulation therapy during pregnancy.[25]

Conclusion

The PMPCs have considerable impacts on maternal-fetal morbidity and mortality. The association of inherited thrombophilia and PMPCs has been reported in some studies. Anticoagulation therapy can improve pregnancy outcome in women with previous PMPCs, with or without inherited thrombophilia. Inherited thrombophilia screening tests is not indicated in every woman with previous PMPC.

Conflict of Interest: None declared.

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