Original Article

The Association of Thrombophilia with Fetal Growth Restriction

Ashraf Jamal MD•[1], Sedigheh Hantoshzadeh MD[2], Homa Hekmat MD[1], Shahed Abbasi MD[1]

Abstract

Background: Thrombophilia or the tendency for thrombosis has been linked to pregnancy complications, which include fetal growth restriction. The aim of the present study was to determine the association of maternal thrombophilias with unexplained fetal growth restriction.

Methods: Inherited and acquired thrombophilias were checked in 34 women whose pregnancies were complicated by fetal growth restriction and 68 women with normal growth fetuses as controls, 8 – 10 weeks postpartum. Cases were matched for age, body mass index, and parity with two healthy women who had normal pregnancies during the same time period. Exclusion criteria were: maternal vascular disease, structural malformations, chromosomal abnormalities, cytomegalovirus infection, and history of drug abuse. Intrauterine growth restriction was diagnosed when the fetal weight or birth weight was below the 10th percentile for gestational age.

Results: The prevalence of all thrombophilia was 55.9% in the case group compared with 10.3% in the control group (P<0.001; OR: 11; 95% CI: 3.9 – 31.1). The prevalence of thrombophilic mutations were significantly higher in the case group compared with the control group (P=0.016; OR: 14.4; 95% CI: 1.7 – 124.8). The frequency of other types of inherited or acquired thrombophilias were significantly higher in fetal growth restriction cases than controls (P<0.001; OR: 9.9; 95% CI: 3.2 – 30.9). Protein S deficiency was the most common thrombophilic defect in the fetal growth restriction group (41.1%) compared with 2.9% of controls (P<0.001). A significant difference in the frequency of multiple thrombophilias was noted between the two groups (P<0.001). All cases that had a history of fetal growth restriction during their previous pregnancies were positive for thrombophilic defects.

Conclusion: Fetal growth restriction pregnancies have a higher prevalence of thrombophilias.

Keywords: adverse pregnancy outcome, fetal growth restriction, inherited and acquired thrombophilia

Authors' affiliations: [1]Department of Obstetrics and Gynecology, Perinatology Division, Shariati Hospital, Tehran University of Medical Sciences, Tehran, [2]Department of Obstetrics and Gynecology, Perinatology Division, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
•**Corresponding author and reprints:** Ashraf Jamal MD, Department of Obstetrics and Gynecology, Perinatology Division, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Tel: +98-218-490-2415, E-mail: jamalsh@tums.ac.ir
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Introduction

Fetal growth restriction (FGR) is a complex challenge in perinatal medicine. It is associated with increased perinatal mortality and morbidity. Additionally, the risk of abnormal neurological development and adverse long-term consequences is significantly increased compared with appropriately grown fe-

tuses. Research for understanding and preventive modalities in this issue is of value. Recently, considerable attention has been paid to a possible association between some obstetrical complications and thrombophilias.[1,2] Pathophysiological mechanisms in thrombophilia appear to be intervillous thrombosis and impaired placental perfusion. Some studies have shown a positive association between thrombophilia and FGR,[3] while other analyses have demonstrated no association between thrombophilia and adverse pregnancy outcomes.[4] Considering the conflicting results and different frequencies of thrombophilic defects among various populations,[5] this case-control study was designed to determine the association between thrombophilias and FGR.

Patients and Methods

We studied 34 consecutive women with singleton pregnancies complicated by FGR and 68 women who gave birth to normal weight newborns during the same time period. FGR was defined as fetal weight less than the 10th percentile according to the Practice Bulletin of ACOG[6] and diagnosed by serial ultrasonography, six weeks to three days prior to delivery. Cases with fetal congenital malformations, chromosomal abnormalities, maternal vascular diseases, cytomegalovirus infection, and history of drug abuse were excluded. Case and control groups were matched for age, body mass index (BMI), and parity. The study was approved by Institutional Review Board and informed consent was obtained from all participants. All participants were tested 8 – 10 weeks postpartum for a mutation in the factor V gene (factor V Leiden), prothrombin gene 20210 (PGM), MTHFR T677 and deficiencies of protein C, protein S, antithrombin, and the presence of antiphospholipid antibodies, including anticardiolipin antibodies and lupus anticoagulant. Thrombophilic mutations were detected with DNA analysis (PCR); plasma protein S was measured with specific enzyme-linked immunosorbent assay (ELISA; Stago Co., France). Protein C and antithrombin activity were determined by chromogenic assay (Stago Co., France). Levels of IgG and IgM anticardiolipin antibodies were determined with ELISA (Orgentec Co., Germany). The presence of lupus anticoagulant was detected with a clotting assay (Stago Co., France).

For statistical analysis, the Statistical Package for Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) program was used. Data distribution was assessed by the one sample Kolmogorov-Smirnov test. Age and BMI displayed a normal distribution and were presented as mean (±SD) and compared with independent *t*-test. The other variables were nonparametric and shown as a median (range). The Mann-Whitney U test was used to assess differences between groups, as needed. Qualitative variables were expressed as numbers (%) and compared with the Chi-square and Fisher exact tests when appropriate. The backward conditional binary logistic regression analysis was performed to calculate the odds ratio (OR), adjusted for matching factors. Significance was set at $P<0.05$.

Results

The groups were well matched with respect to age, BMI, and parity (Table 1). There were 11 and 21 primiparous women in the case and control groups, respectively. The gestational age at delivery and birth weight were significantly lower in the case group (Table 1). Ten of 23 multiparous women in the case group had a previous history of IUGR. In the control group, there was no IUGR history noted. Overall, six women (17.7%) in the case group had at least one of three thrombophilic mutations, as compared with one (1.5%) in the control group (OR: 14.4; 95% CI: 1.7 – 124.8; $P=0.016$). Additionally the frequency of other types of inherited or acquired thrombophilias was significantly higher in the case group (44.1%) compared with 7.4% in the control group (OR: 9.9; 95% CI: 3.2 – 30.9; $P<0.001$) (Table 2). Protein S deficiency was the most common thrombophilia and was found in 14 of 34 women (41.2%) with IUGR compared to 2 out of 68 women (2.9%) with normal pregnancies ($P<0.001$). The prevalence of all thrombophilia was 55.9% in the case group compared with 10.3% in the control group (OR: 11; 95% CI: 3.9 – 31.1; $P<0.001$). Eight women with IUGR and one woman in the control group had multiple thrombophilias (OR: 32.5; 95% CI: 3.8 – 280.5; $P=0.002$) (Table 2).

Each of the women with multiple thrombophilias was considered once for statistical analysis. Thrombophilia was found in all ten multiparous women with FGR who had previous histories of FGR. Placental abruption occurred in seven women in the case group and none in the control group ($P<0.001$); all were positive for thrombophilia. Only one intrauter-

Table 1. Clinical characteristics in case and control groups

	Case group (*n*=34)	Control group (*n*=68)
Age (years)†	27.7(±5.3)	27.3(±5.9)
BMI†	25.1(±3.6)	25.4(±3.5)
Parity†	2(1 – 5)	2(1 – 5)
Gestational week at delivery*	36(25 – 39)	39(37 – 42)
Birth weight (grams)*	2200(450 – 2450)	3100(2700 – 3700)

Data are presented as mean (±SD) or median (range); †Matching factors; **P*<0.001(Mann Whitney U test)

Table 2. Prevalence of inherited and acquired thrombophilias in the case and control groups

Type of thrombophilia	Case group (*n*=34) number (%)	Control group (*n*=68) number (%)	Odds ratio (95% CI)	*P*-values
Inherited:				
MTHFR +/+ or -/+ *	4(11.8)	1(1.5)	8.9(0.95 – 83.3)	0.055
Factor V Leiden +/+ or -/+ **	2(5.9)	0	Non-applicable	—
Total	6(17.7)	1(1.5)	14.4(1.7 – 124.8)	0.016
Acquired or inherited: deficiency of protein C, protein S or antithrombin or presence of anticardiolipin antibodies	15(44.1)	5(7.4)	9.9(3.2 – 30.9)	<0.001
All thrombophilias	19(55.9)	7(10.3)	11(3.9 – 31.1)	<0.001
No thrombophilias	15(44.1)	61(89.7)	Reference	
Single thrombophilias	19(55.9)	7(10.3)	7.5(2.4 – 23.4)	0.001
Multiple thrombophilias	8(23.5)	1(1.5)	32.5(3.8 – 280.5)	0.002

MTHFR=methyltetrahydrofolate reductase; CI=confidence interval; +/+=homozygote; -/+=heterozygote; *Among the cases, three were heterozygotes and one was a homozygote for MTHFR; one woman with this mutation in the control group was heterozygote; **One homozygote and one heterozygote with abnormal activated protein C resistance

ine death and one neonatal death were observed in the case group. The former had combined Protein S and C deficiency, and the latter was a homozygote for the MTHFR mutation. The 19 women diagnosed with FGR and thrombophilia delivered infants with lower median birth weights (1700 g; range: 450 – 2450 g) than those 15 women with FGR and no thrombophilia (2300 g; range: 1800 – 2450 g; *P*=0.003).

Discussion

Although there are increasing prospective studies with sufficient power related to the association between various thrombophilia and obstetrical complications, controversy still remains regarding screening for thrombophilia in women with histories of adverse pregnancy outcomes. Routine screening is not cost-effective and justified. On the other hand, clinicians need guidelines for screening. Guidelines regarding this issue should be prepared according to the frequency of thrombophilic defects in the same population. In this case-control study, we tested two groups of women for inherited and acquired thrombophilias postpartum. Our results showed a high prevalence (55.9%) of thrombophilia in FGR pregnancies compared with 10.3% in the normal control group. This finding is consistent with a recent systematic review of ten case-control studies that showed a significant association between FGR and thrombophilia[7] but inconsistent with a study by Infante-Rivard et al.[8] who did not find an association between maternal or newborn thrombophilia and FGR.

The difference in the prevalence of genetic thrombophilic mutations (FVL and MTHFR) between the two groups in our study was significant statistically, but the lack of prothrombin gene mutation in our study did not allow any definite conclusion about hereditary thrombophilia. A recent meta-analysis has reported a statistically significant association between factor V Leiden and FGR.[9] However, inclusion of the 10th percentile FGR pregnancies is the first limitation of our study. It seems inclusion of severe FGR cases

have higher chances to be screen positive as Kupferminc et al.[10] have tested severe mid-trimester FGR and shown a strong association between IUGR and thrombophilia.

Protein S deficiency was the most common thrombophilic factor found in 14 of 34 women with FGR compared with 2 out of 68 women with normal pregnancies. We also looked for the frequency of multiple thrombophilia in this study and reached significant difference between two groups. Thrombophilia was found in all ten multiparous women with FGR who had a previous history of FGR. Placental abruption occurred in seven women in the case group and none in the control group, all of which screened positive for thrombophilia. This association has been shown in studies relating to thrombophilia and pregnancy complications.[11]The second limitation in this study is that we did not test for thrombophilia in fetal circulation, whereas some researchers have investigated the role of fetal thrombophilia in the development of adverse pregnancy outcomes, including CP.[12]

In conclusion, we found an association between thrombophilia and unexplained FGR. Therefore, thrombophilia work-up and possibly therapeutic intervention may be recommended in the evaluation and management of women who experience FGR.

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