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The relationship between thrombophilia and intrauterine growth restriction

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Approximately 0.7 to 2% of the general population have thrombophilia, but it is estimated that intrauterine growth restriction (IUGR) is due to thrombophilia in 35% of cases. Although the role of thrombophilia in IUGR is not completely known but its destructive effect on placental vasculature is the pathophysiologic cause of defect in transfer of oxygen for fetal growth. The aim of the present study was to determine the role of thrombophilia in fetal growth. This was a case-control study with prospective enrollment. In this study, sera from 43 pregnant women with IUGR and 20 pregnant women with appropriate fetal growth as control were tested for thrombophilia polymorphism (protein S, protein C, factor V leiden, antithrombin III, homocystein, lupus anticoagulant Ab, Anti caradiolipin Ab). Data collection forms and SPSS software were used for analyses. Of 43 women with IUGR, 13(30.2%) and 1(5%) in the control group had positive results for thrombophilia (P=0. 027, OR=8.23). By using logistic regression test, there was significant relation between thrombophilia polymorphism and growth of femur length. We found correlation between the presence of thrombophilia factor and femur length, but in previous studies thrombophilia was correlated with fetal growth restriction and specific fetal biometry does not mention whether fetal index is under the influence of thrombophilia.

Key words: Thrombophilia, pregnancy, intrauterine growth restriction.

INTRODUCTION

Intrauterine growth restriction (IUGR) is a pathology which is found in 3 to 10% of all pregnancies and is associated with about 20 to 25% of all fetal intrauterine deaths and with long term neurologic sequelae. It presents an increased risk of distress during labor and delivery and a greater risk of perinatal mortality (Severi et al., 2000). Many *ante partum* stillbirths which are currently designnated as unexplained may be avoidable if slow fetal growth could be recognized as a warning sign (Gardosi et al., 1998). In extremely low birth weight infants, IUGR should be considered. These infants have higher morbidity and mortality (Bernstein et al., 2000; Zubrik et al., 2000). Fetuses with IUGR who survive the compromised intra-uterine environment are at increased risk of neonatal morbidity, which includes increased rates of necrotizing enterocolitis, thrombocytopenia, temperature instability and renal failure. Of all fetuses at or below the loth percentile for growth, only approximately 40% are at high risk of potentially preventable perinatal death (Jelhs et al., 2007; Yoshida et al., 2000; Albaiges et al., 2000). Congenital and acquired thrombophilias are the most common predisposing factors for thromboembolism, but they may also contribute to pathophysiological processes involved in recurrent pregnancy loss, fetal death, IUGR (Franchi et al., 2004; Brenner and Aharon, 2007; Kist et al., 2008). Adverse pregnancy outcome in women with thrombophilia is associated with placental vascular damage and impaired gas exchange and reduced blood oxygen carrying capacity and impaired fetal growth (Weiner et al., 2004; Martinelli et al., 2001). So we conducted a study in pregnant women with IUGR to investigate the role of thrombophilia in fetal growth.

MATERIALS AND METHODS

In this case-control study, pregnant women with IUGR were enrolled at the Taleghani Hospital, Shaheed Beheshti Medical

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Table 1. Frequency of thrombophilia in cases and control group.

Thrombophilia/IUGR	Positive (%)	Negative (%)	Total (%)
Positive	13 (30.3)	30 (69.8)	43 (100)
Negative	1 (5)	19 (95)	20 (100)
Total	14 (22.2)	49 (77.8)	63 (100)

Table 2. Comparison between fetal characteristics with thrombophilia.

Fetal index	Thrombophilia	Mean±SD	P-value
Gestational age (week)	Yes	34.46±3.43	>0.05
	No	34.2±2.69	
Fetal weight (g)	Yes	1681±547	>0.05
	No	1475±385	
Head circumference (cm)	Yes	30.5±4.3	>0.05
		30.4±2.5	
Abdominal circumference (cm)	Yes	29.2±5.6	>0.05
	No	28.5±-3.2	
Femur length (mm)	Yes	33.2±5.1	<0.05
	No	50.5±8.8	
Biparietal diameter (mm)	Yes	81.8±2.8	>0.05
	No	80.4±5.1	

Sciences University in Tehran, Iran The study group included 43 pregnant women with IUGR (measured *in utero* by ultrasound and birth weight below loth percentile). The control group consisted of 20 pregnant women with appropriate fetal growth. The number of patients in the Control group is lower than the Case group because the probability of fetal growth restriction is lower in healthy women and doing test for thrombophilia polymorphism is expensive. Patients were tested 8 weeks post partum for protein C, protein S, antithrombin III, factor V leiden, anticardio lipin Ab, lupus anticoagulant Ab, homocystein.

The exclusion criteria were: 1) Heart disease; 2) Diabetes mellitus; 3) Hemoglobinopathy; 4) Cigarette smoking; 5) Drug abuse; 6) Congenital fetal malformation; 7) Multiple pregnancies; 8) Placental abruption; 9) Placenta previa.

Demographic data required including maternal age, gestational age, parity, maternal height and weight were extracted. The results of fetal sonography including biparietal diameter, head circumference, femur length, abdominal circumference, fetal weight and amniotic fluid index were also collected.

Statistical analyses

After data collection, statistical analyses were performed by means of SPSS 15 Software. Fisher exact test for comparing proportions and for mean comparison t-test was also used. The relationship between variables and indices of fetal growth with thrombophilia was investigated by logistic regression test. Individual characteristics of both groups were tested using Chi-square (χ^2). Quantitative variables are reported by mean and standard deviation and for qualitative variables, frequency and ratios are used. P-values of <0.05 were considered statistically significant.

Laboratory evalutaion

Blood samples were drawn from the two groups 8 weeks after delivery. Thrombophilia polymorphism (protein S, protein C, factor V leiden, anti-thrombin III, homocystein, lupus anti coagulant and anti-cardiolipin ab) was checked in a specialized laboratory.

RESULTS

The mean patients` age was 26.2±4.7 in the thrombophilia group and 27.4±5.1 in the Control group. In this study we found that 13 (30.2%) patients with IUGR and 1(5%) with normal fetal growth had thrombophilia (Tables 1 and 2). Ratio comparison was done by using Fisher exact test and was significant (P=0.027); OR in women with IUGR and thrombophilia polymorphism was 8.23. Evaluation of the relationship between thrombophilia polymorphism and fetal biometry in mothers with IUGR comparison was done by logistic regression test. (Tables 3 and 4)

Table 3. Risk of thrombophilia according to maternal characteristic.

Characteristic	Thrombophilia	Mean±SD	P-value
Maternal age (Year)	Yes	26.2±4.7	>0.0.5
	No	27.4±5.1	
Maternal height (cm)	Yes	157.8±4.1	>0.0.5
	No	159.1±5.8	
Maternal weight (kg)	Yes	87.7±6.6	>0.0.5
	No	88.9±7.2	
Gravidity	Yes	1.92±1.6	>0.0.5
	No	1.63±0.85	
Parity	Yes	0.61±1.32	>0.0.5
	No	0.53±0.68	
Symmetrical IUGR	Yes	1.38±0.5	>0.0.5
	No	1.2±0.1	
Amniotic fluid index	Yes	5.1±2.96	>0.0.5
	No	4.86±1.7	

Table 4. Frequency and ratio of thrombophilia polymorphism.

Type	Frequency	Ratio (%)	Cumulative Percent
Protein S	1	7.1	7.1
Protein C	3	21.4	28.6
Antithrombin III	1	7.1	50
Homocystein	3	21.4	71.4
LUPUS anti	1	7.1	21.4
Coagulant			
Anti-cardiolipin	3	21.4	14.3
Factor V Leiden	2	14.3	42.9
Total	14	100	

According to this test the association between thrombophilia and femur length was significant ($p<0.001$).

DISCUSSION

By studying pregnant women with IUGR admitted in Taleghani Hospital, we concluded that there was association between thrombophilia and IUGR such that IUGR is increased 8 times in women with thrombophilia polymorphism. This finding was corresponded with some previous studies in which they found independent association between mutation of factor V leiden and prothrombin with the occurrence of fetal growth restriction (Martinelli et al., 2001; Peeters, 2001; Yerspyck et al., 2004). Also we found that maternal thrombophilia was associated with decrease in fetal femur length about 17 times in comparison with the control group. In our study most of the prevalence was in protein C, homocystein and anti-cardiolipin that were associated with IUGR, but in the study done by Polzin and colleagues (1992), they reported that there is significant association between the presence of maternal anti-cardiolipin antibodies and fetal growth restriction. In contrast, in the study done by Claire infant (2002), no association of thrombophilia polymerphism is found with IUGR. According to these studies

therefore, although there is strong association between thrombophilia and poor pregnancy outcome, there is no evidence to support routine screening of all pregnant women for thrombophilia (Alfirevic et al., 2002).

Conclusion

There was association between maternal thrombophilia polymorphism and IUGR asymmetry, such that the growth of femur length was under the influence of thrombophilia factors and other biometric indices were not affected. Therefore we can suggest that thrombophilia polymorphism has more effect on some biometric indices, and more researches are necessary with more cases. The knowledge gap here is about the relationship between thrombophilia polymorphism and the height in adulthood. This question should be answered in future researches.

LIMITATIONS

The control sample size for this study was small due to the high cost of carrying out thrombophilia panel for normal population.

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