Frequency of Genetic Thrombophilia in Severe Intrauterine Growth Restriction

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Abstract

Objective: To investigate the frequency of genetic thrombophilia in pregnancy complicated with severe intrauterin growth restriction in which absent or reversed end-diastolic blood flow were detected.

Methods: We presented 17 cases with diagnosed as severe intrauterine growth restriction with absent or reversed end-diastolic blood flow and the test result of genetic thrombophilia (activated protein C resistance, protein C, free protein S antigen) were available.

Results: Genetic thrombophilia was detected in 11 (%64.7) cases. In three cases (%17.6), two factor were estabilished. These ratios were higher than the incidence for the normal population.

Conclusion: It seems that the frequency of genetic thrombophilia was increased in severe intrauterine growth restriction.

Keywords: Thrombophilia, intrauterine growth restriction, Doppler, pregnancy.

Şiddetli intrauterin gelişme yetersizliği olgularında genetik trombofili sıklığı

Amaç: Umbilikal arterde diyastol sonu akım kaybı veya ters akım saptanan şiddetli intrauterin gelişme yetersizliği (IUGY) olgularında trombofili sıklığını saptamak.

Yöntem: 2003-2005 tarihleri arasında umbilikal arterde diyastol sonu akım kaybı veya ters akım saptanan ve genetik trombofili testleri yapılmış (aktive protein C rezistansı, protein C aktivitesi, serbest protein S antijenitesi) şiddetli intrauterin gelişme yetersizliği saptanan 17 olgunun sonuçları incelendi.

Bulgular: Onbir vakada (%64.7) trombofili saptandı. Üç olguda (%17.6) iki faktör pozitifliği mevcuttu. Bu oranlar normal toplum için bildirilen değerlerden yüksektir.

Sonuç: Şiddetli intrauterin gelişme yetersizliği saptanan olgularda daha yüksek oranda genetik trombofiliye rastlanabilir.

Anahtar Sözcükler: Trombofili, intrauterin gelişme yetersizliği, Doppler, gebelik.

Introduction

Genetic thrombophilia is used to define a group of genetic hypercoagulability disorder that can cause thrombosis. Factor V Leiden (FVL), methylenetetrahydrofolate reductase, prothrombin G20210A mutations and protein C, protein S and antithrombin III deficiencies are commonly specified from this group. Recent studies give rise to thought that there may a relationship between

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genetic thrombophilia and obstetric complications.[1] There are many retrospective and some prospective studies about the relationship between genetic thrombophilia and intrauterine growth restriction in the literature. But these studies is a heterogenic group because methods selecting the patient and number of patients; the results disagree with each other. Publications that examine the relationship between intrauterine growth restriction and genetic thrombophilia whose number of case is relatively low give rise to thought that genetic thrombophilia can be one of the reasons for intrauterine growth restriction.[2-8] But this relationship is not observed in the larger series.[9,10]

Infants with low birth weight according to pregnancy week form a heterogenic group. Some group of these infants is unable to develop for the reason of malnutrition reasoning from placental deficiency. Other group includes the healthy infants structurally small and abnormal infants having fetal abnormality, chromosome aberrations or transmitted the intrauterine disease.

It is known that more thrombotic processes are seen more for the cases showing preeclampsia and intrauterine growth restriction than the normal infants in the placenta studies.[11-13] Although there are contrary studies, it is thought that genetic thrombophilia should cause placenta deficiencies and intrauterine growth restriction by causing disorders during placenta thrombosis or placenta formation.[11,12,14-16] But, in almost every case-control cohort and studies examining low birth weights and genetic thrombophilia intrauterine growth restrictions are defined as the cases below the definite percentile fetal weight or standard deviation, cases detected placenta deficiencies are not separately defined. In actuality, most part of the infants being smaller than expected according to the pregnancy week, normal or abnormal, consists of infants structurally small.

Consequences of few studies classifying the cases by naming Doppler in English literature are inconsistent.[5,8] In our study, thrombophilia incidence is stated for some group of low birth weighted infants having diastole end current loss of umbilical artery or inverse current.

Methods

Results relating to 17 patients that the genetic thrombophilia tests were studied and cured for diastole end current loss of umbilical artery or inverse current between the years 2003-2005 are retrospectively evaluated. Examined factors include C resistance, protein C, protein S tests. In addition, lupus anticoagulant and anticardiolipin Ig G, Ig M and anti phospholipids Ig G, Ig M test results were also investigated.

Laboratory Method: Free protein S antigen was measured by colorimetric method using enzyme elinked immunosorbent assay (ELISA) (Asserachrom free protein S, Diagnostica Stago, Asniéres, France) and Protein C Stachrom protein C (Automated Coagulation Laboratory, Diagnostica Stago, Asnieres, France). APC resistance was measured with STA®-Staclot® Protein C kit (PTT-LA Lupus Anticoagulant aPTT-based reagent, Diagnostica Stago, Asniéres, France). Plasma anticardiolipin and anti phospholipids antibody was measured with commercial ELISA kits. Normal values used for abnormal test results are given in the Table 1.

Study does not include a control group. Thrombophilia incidences informed in normal population are used in order make a comparison.[17-19]

Table 1. Reference values of the tests.

Test	Positive value
APC-R	<120 sn
Pro C	< %60
Pro S	< %40
APTT-LA	>48 sn
Anticardiolipin Ig G	>12 MPLU/m
Anticardiolipin Ig m	>12 GPLU/ml
Antiphospholipids Ig G	>12 RU/ml
Antiphospholipids Ig m	>12 RU/ml

Results

List of the patients are given in the Table 2. Weight of all the infants were under 5% according to their gestation weeks. None of the patients had anti phospholipids antibody syndrome. In 11 of

Tablo 2. List of the patients.

Nr	APC-R	Pro CR	F-Pro S	Pregnancy week	Weight (g)
1	N	N	N	32	900
2	N	N	A	31	850
3	A	N	N	30	950
4	N	N	N	28	600
5	A	N	N	32	1100
6	A	N	A	27	400
7	A	N	A	31	900
8	N	A	N	32	720
9	N	N	N	31	1000
10	N	A	N	32	900
11	N	N	N	33	1200
12	N	N	A	34	1350
13	N	N	A	31	950
14	N	N	N	33	1200
15	A	N	A	33	1050
16	N	N	N	32	900
17	N	N	A	31	900

N: normal, **A:** abnormal

the patients at least one (64.7%), in three of them two genetic thrombophilia were seen (Table 3). When it is compared with the ratios declared for the normal society, the ratio of thrombophilia was significantly higher for the patients in the work group (Table 3). The fourth, 6th, 7th and 8th cases there were intrauterin exitus. Interestingly, three of these cases, thrombophilia were detected (6th, 7th and 8th).

Table 3. Test results.

Test	Case n (%)	Normal population (17-19)%
APC-R	5 (29.4)	<15
Pro C	2 (11.8)	0.2-0.4
Pro S	7 (41.2)	0.3-0.13
Toplam	**11 (64.7)**	

Discussion

In our study, at least one thrombophic factor was detected for the cases in a group which intrauterine growth restriction was determined and having diastole end current loss in umbilical artery or inverse current. FVL mutation studies of the patients are not practiced, APC resistance results are available. While APC resistance is monitored in pregnancy especially for the older age pregnancies, VL mutation is detected in most of the cases which APC resistance is determined. 7.1% carrier frequency is declared for the FCL mutation of the Turkish society.[21]

In one of the early studies about the issue, Kupferminc et al detected at least one thrombophilia as a ratio of 50% in 44 intrauterine growth restriction cases.[2] In this study, 66% of the infants were born before 36th week and average infant weight was 1387 g Kupferminc et alcompared a case having placenta deficiency and serious growth deficiency in the 22-26 pregnancy weeks with 52 normal pregnancies in their later published series. Thrombophilia frequency was 69% for the group having growth deficiency and 14% for the control group. 10 of the 13 infants recorded intrauterin exitus before the 25th pregnancy week had thrombophilia in accordance with our study. While 33% frequency of twice and more thrombophilia factors were detected for the intrauterine growth restriction group, none of the patients in the control group had thrombophilia.

Verspyck et al observed a relationship between intrauterine growth restriction and thrombophilia in a study including 203 infants having a fetal weight below 3%. Interestingly in this study, none of the informed 34 infants having diastole end current loss had thrombophilia factors.[8]

Mc Cowan et al investigated the abnormal Doppler findings detected SGA infants separately in their study including 145 structurally small intrauterine growth restriction cases and 290 normal pregnant.[9] When a general compare is done thought the study, there were no differences between the infants SGA infants and control group about the thrombophilia incidence. But, they declared an increase in the frequency of thrombophilia in a group of abnormal Doppler detected infants especially of the ones having a weight less than 3% although there was no statistically significant difference.

In a recent metaanalysis, the relationship between FVL and prothrombin gene mutation and intrauterine growth restriction is searched.[22] While a statistically significant heterogeneity between the studies included in the metaanalysis was detected, it was stated that there should be a relationship between prothrombin gene mutation and intrauter-

ine growth restriction (OR approximately 2.4). Interestingly, when intrauterine growth restriction diagnosed series were separately evaluated for the fetal weights under 10 and 5%, relationship between FVL/prothrombin gene mutation and intrauterine growth restriction existed only for the series having the fetal weights under 5%. When it is considered that the cases of severe intrauterine growth restriction developed depending on the placenta deficiency are most commonly seen for the group having the fetal weights under 5%, it is seen that there should be a relationship between severe intrauterine growth restriction and FVL and prothrombin gene mutation.

In the present literature, there is no evidence supporting the routine thrombophilia scanning for the pregnancies which severe intrauterine growth restriction is detected. We believe that the separate classification of he cases which placenta deficiency is detected will help to clarify the subject.

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