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Intrauterine growth restriction and genetic predisposition to thrombophilia

FRANCA FRANCHI
IRENE CETIN
TULLIA TODROS
PATRIZIO ANTONAZZO
MARIA S. NOBILE DE SANTIS
SIMONA CARDAROPOLI
PAOLO BUCCIARELLI
EUGENIA BIGUZZI

A B S T R A C T

Background and Objectives. Intrauterine growth restriction is an important cause of morbidity and mortality. Its pathogenesis is still a matter of debate. The aim of this study was to evaluate the association between intrauterine growth restriction (diagnosed *in utero* by serial ultrasound examinations and characterized by abnormal umbilical arterial Doppler velocimetry) and thrombophilic polymorphisms (factor V Leiden, prothrombin G20210A) or methylenetetrahydrofolate reductase C677T carried by mothers and/or neonates.

Design and Methods. This was a case-control study with prospective enrollment. Fetuses with intrauterine growth restriction were included if they had three characteristics: 1) reduced intrauterine growth (measured *in utero* by ultrasound); 2) birth weight below the 10th percentile; 3) abnormal Doppler velocimetry of the umbilical artery. The three polymorphisms were evaluated in 48 cases and in 98 controls by polymerase chain reaction (PCR) and restriction analysis.

Results. Factor V Leiden was present in 2/48 (4%) mothers or neonates among cases and 7/98 (7%) among controls. Prothrombin G20210A was present in 0/48 (0%) mothers or neonates among cases and 4/98 (4%) among controls. Methylenetetrahydrofolate reductase C677T was present in 16/48 (33%) mothers or neonates among cases and 22/98 (22%) controls. Overall the prevalence of the polymorphisms in mothers and/or neonates was 18/48 (37%) in cases and 33/98 (34%) in controls.

Interpretation and Conclusions. No association was found in this study between intrauterine growth restriction with abnormal umbilical blood flow and thrombophilic polymorphisms or methylenetetrahydrofolate reductase C677T.

Key words: intrauterine growth retardation, thrombophilia, Doppler ultrasound.

From the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre and Department of Internal Medicine, IRCCS Maggiore Hospital, University of Milan, Italy (FF, PB, EB); Obstetrics and Gynecology, DMCO San Paolo, University of Milan, Italy (IC, PA, MSNdS); Unità di Medicina Materno-Fetale, University of Turin, Italy (SC).

Correspondence: Eugenia Biguzzi, Angelo Bianchi Bonomi Haemophilia and Thrombosis Center, via Pace 9, 20122 Milan, Italy.
E-mail: eugeniabiguzzi@yahoo.it

Pregnancy may be complicated by several diseases such as hypertension, pre-eclampsia, HELLP, intrauterine growth restriction and fetal loss. These complications can evolve into each other and their pathogenesis is still a matter of debate. Intrauterine growth restriction is an important cause of morbidity and mortality. Infants with this disorder are likely to develop, later in childhood, neuropsychological defects and suffer educational disadvantages.[1,2] Moreover, there is epidemiological evidence that children whose intrauterine growth was restricted have a higher risk of cardiovascular and endocrine diseases in adulthood.[3] In recent years, the application of new biophysical and biochemical technologies to fetal medicine has greatly improved the diagnosis of intrauterine growth restriction. However, the understanding of its pathogenetic mechanisms is still scanty. It is well known that hereditary thrombophilia is associated with an increased risk of venous thromboembolic events.[4] An association between obstetric complications and heritable causes of thrombophilia has been reported:[5-9] indeed, thrombosis in decidual vessels could cause inadequate maternal-fetal circulation and thus placental insufficiency.

Previous studies on the potential role of prothrombotic risk factors as a possible cause of pregnancy complications have focused mainly on the maternal side of the placenta only. Kupferminc *et al.*[5] reported an association between thrombophilia (factor V Leiden, prothrombin G20210A, methylenetetrahydrofolate reductase C677T) and intrauterine growth restriction (defined as a birthweight below the 5th percentile for gestational age). These results were confirmed by two retrospective studies[7,11] which eval-

uated the same thrombophilic abnormalities in the mothers. However, prothrombotic risk factors in the fetus must be considered as well, given the importance of a hemodynamic balance between maternal and fetal circulations for a normal pregnancy. On this basis, two recent case-control studies[12,13] investigated three polymorphisms (factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T) in low-weight newborns diagnosed at birth and their parents,[12] or in mothers and newborns of normotensive small for gestational age pregnancies.[13] Neither study found an association between intrauterine growth restriction and the polymorphisms, although one of them[13] seemed to suggest an increased risk of intrauterine growth restriction in a subgroup of infants with abnormal umbilical Doppler ultrasound findings.

Umbilical Doppler velocimetry has been shown to be useful in distinguishing fetuses that are small, but otherwise normal, from those that are truly growth restricted, because of an abnormal blood supply to the placenta.[14] Moreover, umbilical Doppler patterns reflect the severity of intrauterine growth restriction: an absent or reversed end diastolic flow is often found in cases with the most severe prognosis, while positive end diastolic flow reflects a better prognosis.[15]

We performed a case-control study with prospective enrollment aimed at evaluating the association between genetic predisposition to thrombophilia (factor V Leiden and prothrombin G20210A) carried by the mothers and/or the newborns and intrauterine growth restriction in a subset of fetuses diagnosed *in utero* and characterized by abnormal umbilical arterial blood flow. The methylenetetrahydrofolate reductase C677T polymorphism was also evaluated in order to be able to compare the results with previous reports, even though this polymorphism is not a proven risk factor for thrombosis.[16]

Whether or not there is a clear association between these polymorphisms and intrauterine growth restriction could be relevant in order to establish the possible role of thromboprophylaxis as early treatment in mothers, which could lead to lower morbidity in the newborn period and to improved long term outcomes. So far, no prophylaxis exists for most cases of intrauterine growth restriction, and timing of delivery is the only available therapy.[10]

Design and Methods

Study population

Consecutive women referred to two University Hospitals (Milan and Turin) who had ultrasound examinations showing patterns of intrauterine growth restriction were eligible for the study. Gestational age was calculated from the last menstrual period and confirmed by an ultrasonographic examination performed before 20 weeks of gestation. Babies were excluded if they showed morphologic malformations at birth. Multiple pregnancies were also excluded from the study.

Fetuses with intrauterine growth restriction were included if they had three characteristics: (i) reduced intrauterine growth (ultrasound measurement of the abdominal circumference below the 10th percentile of reference values;[17] alternatively a percentile reduction >40%, compared to the previous measurement of abdominal circumference); (ii) birth weight below the 10th percentile according to Italian standards for birth weight and gestational age;[18] (iii) abnormal Doppler velocimetry of the umbilical artery.[10]

The percentage reduction of fetal weight was calculated as: % reduction = (expected fetal weight - fetal weight)/expected fetal weight $\times$ 100, where expected fetal weight is the 50th percentile for gestational age and gender.[18] The wave form of the umbilical artery blood flow was obtained with a coaxial pulsed Doppler velocimeter with a sample volume of 5 mm and high-pass filters set at 100 Hz (Ultramark 5, ATL Corp.). The pulsatility index was measured according to the simplified Gosling formula (systolic velocity minus diastolic velocity divided by mean velocity).[19] Umbilical artery Doppler was considered pathological when the pulsatility index exceeded 2 standard deviations above the mean value for gestational age in our reference population.[20] Fetuses with intrauterine growth restriction were classified by type of pathological Doppler, absent/reversed end diastolic flow or positive end diastolic flow and by fetal heart rate recordings performed immediately before delivery. The criteria utilized to evaluate fetal heart rate tracings were the degree of variability, the presence of accelerations from the baseline and the presence of decelerations in heart rate after Braxton Hicks contractions.[10] Fetal heart rate tracings were evaluated independently by two clinicians blind to other information, and defined dubious if these two clinicians did not agree on the classification.

Pregnancy induced hypertension was defined as a blood pressure >140/90mmHg on two or more occasions. Pre-eclampsia was defined as a blood pressure >140/90mmHg on two or more occasions with a rise in diastolic blood pressure > 25mmHg occurring after 20 weeks of gestation together with proteinuria (>0.3 g/24 h or ≥3+ on dipstick testing when delivery precluded a 24h collection).[21] Criteria for the diagnosis of HELLP syndrome included the following laboratory findings in combination: a) hemolysis (lactic dehydrogenase >600IU/L, or serum bilirubin >1.2mg/dL, or the presence of schistocytes in the peripheral blood); b) an increased concentration of serum aspartate aminotransferase (≥ 70 IU/L); c) thrombocytopenia (platelet count <100,000/mm^3). At delivery, maternal blood was

collected from a peripheral vein and fetal blood was withdrawn from a doubly clamped segment of the cord immediately after fetal extraction.

Two control women for every case were recruited in the same obstetric hospitals during the same enrollment period among women who gave birth to healthy neonates with a birth weight between the 10th and 90th percentiles. Women were excluded if they had had obstetric complications, and/or if their babies showed malformations at birth. Multiple pregnancies were also excluded from the study. Non-Caucasian women were excluded from both groups.

The study was approved by the Ethical Committees of the two hospitals and informed consent was obtained from each pregnant woman.

Blood collection and laboratory analysis. Blood samples were collected in sodium citrate from mothers and newborns and stored at –20°C. When neonatal blood was not available, placental tissue (of fetal origin) was collected. DNA was extracted from blood and tissue samples, using the Qiagen QiaAmp DNA kit (Qiagen, Valencia, CA, USA). Factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase C677T polymorphisms were evaluated in the mother and the neonate by PCR and restriction analysis according to previously described methods.[22-24]

Statistical analysis

Continuous variables are expressed as the median and range, categorical variables as percentages. Difference between groups were calculated by χ^2 or Fisher's exact test for categorical variables, and by the Mann-Whitney U test for continuous variables. $p \leq 0.05$ was set as the level denoting statistical significance.

Results

Forty-eight pregnant women with a diagnosis of intrauterine growth restriction and ninety-eight controls were enrolled between October 1999 and October 2002 in two Obstetrics Clinics. The characteristics of the patients and controls are described in Tables 1 and 2. Assuming (i) a prevalence of 3% for factor V Leiden or prothrombin G20210A and of 15% for methylenetetrahydrofolate reductase C677T and a baseline rate of IUGR (with abnormal Doppler velocimetry) of 0.7% in the Italian population and (ii) a power of 80% and an α error of 0.05, this study (48 cases and 98 controls) could have detected a statistically significant odds ratio of 4.5 (for carrying factor V Leiden or prothrombin G20210A) and of 3.0 (for methylenetetrahydrofolate reductase C677T). The genotype distribution for factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase C677T in the control group are consistent with the Hardy-Weinberg equilibrium. The prevalence of the three polymorphisms and the dif-

Table 1. Clinical characteristics of patients and controls.

	Patients n=48	*Controls n=98*	*p*
Gestational age (weeks) median (range)	32.0 (22.0-37.0)	39.2 (37-42)	<0.001
Birth weight (grams) median (range)	1227 (250-2150)	3275 (2500-4020)	<0.001
Pre-pregnancy Body Mass Index: median (range)	22.0 (15.5-43.4)	22.0 (16.7-27.1)	0.024
Maternal age median (range)	31.5 (18-41)	31.5 (21-40)	0.66
Maternal age ≥ 36 years	10/48 (21%)	16/98 (16%)	0.47
Primiparous	30/48 (64%)	61/98 (62%)	0.98
Smoking (>5 cigarettes/day)	5/48 (10%)	2/98 (2%)	0.04
Lupus anticoagulant/ antiphospholipid syndrome	0/48	0/98	n.a*

**not applicable.*

Table 2. Characteristics of cases.

	Patients n=48
Mean % fetal weight reduction (range)	40.1 (12.5-59.9)
Mean head circumference/abdominal circumference ratio (range)	1.21 (1.07-1.6)
Doppler velocimetry	
positive end diastolic flow	27/48 (56%)
absent/reversed end diastolic flow	21/48 (44%)
Fetal heart rate	
Normal	28/48 (58%)
Dubious	4/48 (8%)
Pathological	16/48 (33%)
Pregnancy induced hypertension	10/48 (21%)
Pre-eclampsia	12/48 (25%)
HELLP, Lupus anticoagulant/ antiphospholipid syndrome, autoimmune diseases	0/48
Mean placenta weight (grams)	247 (87-470)

Table 3. Prevalence of heterozygous factor V Leiden, heterozygous prothrombin G20210A and homozygous methylenetetrahydrofolate reductase C677T in mothers and neonates (neonatal blood or fetal placental tissue, when neonatal blood was not available).

	Cases n=48	*Controls n=98*	*p*
V Leiden mothers	2/48 (4.0%)	3/98 (3.0%)	0.66
V Leiden neonates	1/48 (2.0%)	5/98(5.1%)	0.66
V Leiden mothers AND neonates	1/48 (2.0%)	1/98 (1.0%)	0.55
V Leiden mothers OR neonates	2/48 (4.0%)	7/98 (7.1%)	0.72
Prothrombin G20210A mothers	0/48(0%)	2/98 (2.0%)	0.45
Prothrombin G20210A neonates	0/48 (0%)	2/98 (2.0%)	0.45
Prothrombin G20210A mothers AND neonates	0/48 (0%)	0/98 (0%)	n.a*
Prothrombin G20210A mothers OR neonates	0/48(0%)	4/98 (4.1%)	0.30
MTHFR C677Tmothers	10/48 (21%)	14/98 (14%)	0.32
MTHFR C677T neonates	10/48 (21%)	13/98(13%)	0.24
MTHFR C677Tmothers AND neonates	4/48 (8%)	5/98 (5%)	0.69
MTHFR C677T mothers OR neonates	16/48 (33%)	22/98(22%)	0.16
V Leiden OR prothrombin G20210A OR MTHFR C677TTmothers	12/48 (25%)	19/98 (19%)	0.44
V Leiden OR prothrombin G20210A OR MTHFR C677T neonates	11/48 (23%)	20/98 (20%)	0.73
V Leiden OR prothrombin G20210A OR MTHFR C677T mothers AND neonates	5/48 (10%)	6/98 (6%)	0.56
V Leiden OR prothrombin G20210A OR MTHFR C677T mothers OR neonates	18/48 (37%)	31/98 (32%)	0.48

**not applicable.*

ference between groups, calculated by Fisher's exact test, are shown in Table 3. The case and control distributions of maternal and/or neonatal genotypes for factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase C677T were not significantly different. Because of the different prevalences of smokers in the case and control groups, the statistical analysis was also performed on 43 cases and 96 controls after exclusion of smokers (none of whom carried factor V Leiden or prothrombin G20210A). The analysis did not highlight any significant association between factor V Leiden and/or prothrombin G20210A carried by the not-smoking mothers or the newborns and IUGR.

The three polymorphisms were similarly distributed between cases characterized by absent/reversed end diastolic flow (9/21, 43%) and cases with positive end diastolic flow (9/27, 33%), which means that the severity of abnormal Doppler velocimetry (evaluated as absent/reversed end diastolic flow or positive end diastolic flow) does not correlate with the presence of thrombophilic polymorphisms.

Fetal heart rate was normal in 11/18 (61%) cases carrying one of the evaluated polymorphisms, dubious in 2/18 (11%) and pathologic in 5/18 (28%).

Discussion

A high proportion of cases of intrauterine growth restriction have no apparent cause. Placental histomorphologic abnormalities such as fibrin deposits, thrombosis, villous infarcts, fibrosis and hypovascularity are well documented in intrauterine growth restriction[25,26] and they are associated with altered blood perfusion on both the maternal and the fetal side of the placenta.[27] The hypothesis of a pro-thrombotic alteration, as a possible cause of intrauterine growth restriction, is appealing, because it might offer a possible therapeutic approach to a disease that, up to now, has premature delivery as the only possible method to avoid death *in utero*. The thrombophilic defects might cause intrauterine growth restriction as a consequence of insufficient nutrition, due to inadequate placental circulation. The clinical variability of intrauterine growth

restriction may depend on the severity of placental alterations associated with thrombophilic defects carried by the mother, the newborn or both.

This is the first study which evaluated two thrombophilic polymorphisms (factor V Leiden and prothrombin G20210A) and methylenetetrahydrofolate reductase C677T in mothers and newborns of pregnancies complicated by intrauterine growth restriction diagnosed *in utero* and characterized by abnormal Doppler velocimetry of the umbilical artery. Although methylenetetrahydrofolate reductase C677T is not associated with an increased risk of thrombosis, this polymorphism was included in the study in order to compare the results with those of previous studies.[16]

The selection of this group of fetuses with intrauterine growth restriction was thought to offer a better possibility of highlighting any association with the polymorphisms. Even though the prevalence of the defects in the control group was what would be expected in the Italian population,[28] this study found no association between intrauterine growth restriction and the three polymorphisms carried by mothers or newborns. Moreover, the prevalence of the polymorphisms was similar in the groups with absent/reversed end diastolic flow and positive end diastolic flow, further suggesting that even the very severe cases of IUGR are not associated with an increased risk of thrombophilia. However, because of the low prevalence of these polymorphisms in the Italian population, the present study would only have been able to highlight a strong association with intrauterine growth restriction, and larger studies are necessary to exclude a weaker association and confirm the results.

A potential limitation of this study is the higher prevalence of smokers among cases than among controls. Nevertheless, a separate analysis performed on not-smoking cases and controls, did not show any significant association between IUGR and thrombophilic polymorphisms (factor V Leiden and/or prothrombin G20210A).

These data confirm the large case-control hospital-based study by Infante Rivard.[12] However, it is important to underline the differences between the two studies. The present study considered cases with intrauterine growth restriction, defined as low birthweight associated with reduction of fetal growth demonstrated *in utero,* and abnormal Doppler velocimetry; the Canadian study considered all newborns below the 10th percentile as cases, thus defining a heterogeneous population comprising neonates with true intrauterine growth restriction and small, but otherwise normal, babies. The control population also differs in the two studies: the Canadian study matched cases and controls for gestational age. This means that 17% of the two groups were born between 25 and 35 weeks of gestation. In contrast, in our study, controls were born at term, between 37 and 42 weeks of gestation. Mc Cowan *et al.*[13] also studied a heterogeneous population, finding no association between thrombophilic polymorphisms and small-for-age pregnancies. In their study, the analysis of 25 cases characterized by abnormal umbilical artery Doppler evaluation showed a trend toward an association with thrombophilic polymorphisms. Our study did not confirm this observation.

From a clinical point of view, our results do not support the usefulness of evaluating thrombophilic polymorphisms in pregnant women with previous or current intrauterine growth restriction, nor do they justify the use of anticoagulants as possible prophylaxis against intrauterine growth restriction development in carriers of factor V Leiden, prothrombin G20210A, or methylenetetrahydrofolate reductase C677T. The issue of antithrombotic prophylaxis for women with thrombophilia and pregnancy complications is currently object of debate.[29,30] It is possible that part of the difficulty in finding clear answers to this issue is due to the rarity of some pregnancy complications (pre-eclampsia, IUGR, recurrent miscarriage, late fetal loss), so that many studies consider them together in order to get sufficiently large numbers for a statistical analysis. However, it is possible that these complications reflect different pathogeneses and, therefore, would benefit from different therapeutic approaches.

Nevertheless, it cannot be forgotten that it is very difficult for clinicians to deal with the emotional aspects of intrauterine growth restriction given that no therapy is so far available, except early delivery in the case of fetal distress. Women do very often ask for medications in the case of pregnancy complications, without considering possible side effects. This is very understandable and they can hardly be blamed, taking into account their anxiety. New innovative studies, aimed at evaluating the pathogenesis of intrauterine growth restriction and potential new therapeutic approaches, are necessary.

All the authors meet the authorship criteria (study design, data interpretation, paper writing or revision) and approved the paper final version of the paper. In detail, FF and EB were responsible for the polymorphisms analysis. PB performed the statistical analysis. IC, TT, PA, MSNdS, SC selected all the cases and performed the Doppler and ultrasound evaluations. We thank Dr. EM Faioni and Dr. I Martinelli for helpful discussion. The authors reported no potential conflicts of interest.

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