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Original Article

Obstetric implications of fetal inherited thrombophilia in thrombophilic women

F. Bellussi [a], E. Contro [a], C. Legnani [c], S. Galletti [b], A. Cosentino [b], N. Rizzo [a], T. Ghi [a,*]

[a] Department of Obstetrics and Gynecology, St. Orsola Malpighi University Hospital, University of Bologna, Bologna, Italy
[b] Department of Preventive Pediatric and Neonatology, St. Orsola Malpighi University Hospital, University of Bologna, Bologna, Italy
[c] Department of Angiology and Blood Coagulation, St. Orsola Malpighi University Hospital, University of Bologna, Bologna, Italy

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ABSTRACT

Objectives: The relationship between fetal thrombophilic polymorphism and adverse pregnancy outcomes is still unclear. The aim of this study is to evaluate if fetal thrombophilia may affect obstetric and perinatal outcomes in thrombophilic women.
Study design: From 2007 to 2011 all patients with a known inherited thrombophilic mutation consecutively admitted to our labor ward at $\geqslant$25 weeks of gestation with a singleton viable pregnancy were considered eligible for the purpose of the study. At the age of 1 year, the infants were tested for inherited thrombophilic mutations. Patients were then divided into two groups according to the presence or absence of any neonatal mutation.
Main outcome measures: The following outcome variables were then compared between the two groups: gestational age at delivery, birth weight, incidence of hypertensive disorders of pregnancy and SGA neonates.
Results: Overall, 67 pregnancies of 49 women were studied. Among them, the G20210A Prothrombin (32/67 or 47.7%) mutation and the Factor V Leiden mutation (31/67 or 46.3%) were the commonest findings, with a single patient presenting both. A thrombophilic mutation was found in 38 mother–infant pairs. The risk of all maternal and perinatal events including the incidence of hypertensive disorders disorders (5/29 or 17.2% vs 6/38 or 15.7% $p = 1.00$) and of SGA neonates (3/29 or 10.3% vs 7/38 or 18.4%, $p = 0.49$) was comparable between the two groups irrespective of the associated fetal thrombophilia.
Conclusions: Our data suggest that women with inherited thrombophilia carrying a thrombophilic fetus are not at increased risk of adverse pregnancy outcomes.

Introduction

Inherited thrombophilia is a common condition, whose prevalence in western population is at least 15% [1–3].

The most common thrombophilia polymorphisms are AT III, protein C and protein S deficiencies, factor V Leiden and prothrombin G20210A gene mutations [1,2]. Clinical implications of these conditions among pregnant women are still unclear. Some studies in the past had shown a significant association between maternal thrombophilia and adverse pregnancy outcomes, including mostly fetal demise, hypertensive disorders, fetal growth restriction or placental abruption [4–11]. However, large prospective series and meta-analyses demonstrated that the risk of complications among women with known thrombophilia was not increased [12–19]. In particular, the majority of thrombophilic polymorphisms among women at their first pregnancy did not seem to confer an increased risk of poor obstetric outcomes [20]. On the other hand the occurrence of serious maternal or fetal events has been found significantly increased among a specific subset of patients, such

* Corresponding author. Tel.: +39 0516364411.
E-mail address: tullioghi@yahoo.com (T. Ghi).

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as those with a previous history of obstetric complications [21,22].

Some authors have recently suggested that fetal inherited thrombophilia may actively contribute to adverse pregnancy outcomes [23–27]. In these cases, an increased risk of microthrombosis on the fetal placental surface has been speculated as the mechanism leading to pregnancy complications. However, the association between fetal thrombophilia and obstetric complications is still debated [25,28,29].

The purpose of this study was to assess if the combination of fetal and maternal inherited thrombophilia may worsen pregnancy outcomes in comparison with pregnancies with exclusive maternal thrombophilia.

Materials and methods

This was a prospective observational cohort study. From 2007 to 2011 all patients with a known inherited thrombophilic mutation admitted to our labor ward at $\geqslant$25 weeks of gestation with a viable singleton pregnancy were considered eligible for the study purpose. Thrombophilic mutations considered as inclusion criteria were: Factor V Leiden or prothrombin G 20210 mutations; protein S, Antithrombin III and Protein C deficiencies. Mothers were asked to submit their infants to inherited thrombophilic mutation testing when they were at least 1 year old. Thrombophilic mutations tested were: Factor V Leiden mutation, prothrombin G20210A mutation, Antithrombin III, Protein S and protein C deficiencies. Blood samples were collected in the Department of Preventive Paediatric and Neonatology, St. Orsola Malpighi University Hospital of Bologna and all the assays were performed in the Department of Angiology and Blood Coagulation in the same hospital.

Blood was collected from antecubital vein into 0.109 mmol/L trisodium citrate; plasma was prepared by centrifugation for 20 min at 2000*g* at room temperature; plasma and blood for DNA extraction aliquots was snap frozen and stored at −70 °C. Factor V Leiden and prothrombin G20210A mutations, Antithrombin (activity and antigen), Protein C (activity and antigen) and Protein S (activity, free and total) were performed using standard methods, as previously described [30].

The study was approved by the Local Ethics Committee. Thromboprophylaxis administration during pregnancy according to local protocol was recorded.

Patients with any of the following conditions were excluded: intrauterine fetal death, aneuploidies or congenital anomalies, multiple pregnancies, infectious diseases, chronic hypertension and maternal chronic disorders, drug abuse.

Pregnancies were then divided into two groups according to the presence of neonatal thrombophilia and the following outcome variables were compared between the two groups: gestational age at delivery, birth weight, occurrence of hypertensive disorders of pregnancy (pre-eclampsia, HELLP syndrome, gestational hypertension) or SGA neonates, placental abruption, neonatal admission to NICU.

Statistical analysis

Data are reported as means and standard deviations (SD). Continuous variables were evaluated using Student's *t*-test. Frequencies of occurrence of the primary outcome of interest (IUGR) were stratified according to generated subcategories of thrombophilic polymorphisms. A two-tailed *p*-value less than 0.05 was considered significant. Categorical variables were evaluated using the Fisher exact test. SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and two-tailed $p < 0.05$ was considered statistically significant.

Results

Between January 2007 and January 2011, 18,745 deliveries were recorded at the labor ward of our University Hospital. During this period 258 pregnancies (1.38%) with known maternal inherited thrombophilia were identified from our medical records. From this group 191 cases were excluded due to the following conditions: multiple gestation ($n = 13$); congenital anomalies ($n = 13$); denied consent to neonatal investigations ($n = 76$), maternal drug abuse ($n = 5$), serious coexisting maternal conditions ($n = 39$); lost to follow up ($n = 46$). Overall, 67 pregnancies, obtained in 49 women with inherited thrombophilia, were included in our study population. In all these cases, postnatal assessment of fetal inherited thrombophilia was performed and made available.

Demographic characteristics of pregnancies with exclusive maternal thrombophilia (group A) and of those with fetal and maternal thrombophilia (group B) are shown in Table 1. No significant differences were found between the two groups regarding age, cigarette smoking, race and BMI, whereas women without a thrombophilic fetus were more frequently exposed to Low Molecular Weight Heparin (LMWH) (17/29 or 58.6% vs 12/38 or 31.5% respectively, $p = 0.046$). The prevalence and type of inherited thrombophilic mutations among mothers and neonates are shown in Table 2. No case of maternal or fetal homozygous mutation was observed in our series whereas a double polymorphism was registered only in two women. Clinical details of pregnancies with exclusive maternal thrombophilia (group A) and of those with fetal and maternal thrombophilia (group B) are shown in Table 3.

No significant difference was observed between the two groups in the pregnancy outcomes, including gestational age at delivery (37.52 ± 0.76 vs 38.68 ± 2.57 weeks, $p = 0.13$), birth weight (3014 ± 819 vs 3107 ± 645 gr, $p = 0.60$), incidence of SGA neonates (3/29 or 10.3% vs 7/38 or 18.4%, $p = 0.49$) and maternal hypertensive disorders (5/29 or 17.2% vs 6/38 or 15.7% $p = 1.00$). No cases of admission to NICU were recorded.

More interestingly the rate of IUGR was higher than the overall 13% estimated in our series in those cases with both maternal and fetal prothrombin mutation (18.8%) and with a maternal Protein S ± fetal protein S mutation (31.7%). Therefore we speculate that such patterns are associated with a higher rate of IUGR.