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Prevalence and significance of inherited thrombophilia in pregnant patients presenting with intrauterine growth restriction

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Abstract

This study was undertaken on order to determine if pregnant patients should undergo tests for inherited thrombophilia when intrauterine growth restriction (IUGR) is present. We conducted a study including 343 patients with singleton pregnancy, at the Obstetrics and Gynecology Clinic of the Bucharest University Emergency Hospital, Romania from October 2015 till October 2016, researching and analyzing the correlations between inherited thrombophilia and IUGR, using ultrasound evaluation and blood test samples, as thrombophilic mutations may be a cause for IUGR due to inadequate placental circulation. The patients were distributed in two groups, one comprising patients with no clinical or ultrasonographical signs of IUGR and the other consisting of 29 patients with IUGR, with birth weight below the 10th percentile for the given gestational age. We concluded that MTHFR C677T gene mutation and Factor V Leiden were associated with an increased risk of IUGR, being up to 3 times more prevalent in mothers with fetuses affected by IUGR. Our recommendation states that pregnant patients should undergo tests for inherited thrombophilia when IUGR is present.

Keywords: *thrombophilia, pregnancy, intrauterine growth restriction*

Introduction

Intrauterine growth restriction (IUGR) represents a frequent cause of perinatal morbidity and mortality[1] and is defined as a failure to achieve the standard-target growth for the given fetal development and often appears secondary to placental insufficiency. The incidence is estimated to be about 3% of all pregnancies[2] and it may be associated with adverse neurological, cognitive development, cardiovascular or endocrine health consequences later in life[3-5]. Among the factors that are responsible for IUGR, more than two decades ago, one-third of the total cases were known to be determined by genetic variables, about two-thirds by environmental factors, but there are also the cases where no underlying pathology can be identified[1]. Nowadays, the known causes comprising in fetal (chromosome disorders, congenital anomalies, infections), maternal (genetic factors) and placental factors explain most of the occurrences of IUGR, still in about 25% of them the causes remain unknown[6].

Usually is defined as the statistical deviation of the fetal size from a population based reference, with the threshold established at the 10th or 5th percentile and it is important to differentiate it from small for gestational age (SGA) which means a constitutionally small but healthy fetus[7] that appears to present with a perinatal outcome similar to those of normally grown fetuses.

This disorder is divided in early-onset growth restriction that represents about 20% to 30% of the total cases, with more severe fetal deterioration that can lead in many cases even to fetal death before term, compared to late-onset growth restriction, representing the rest of the cases. Even though milder, it does not exclude the risk of acute severe deterioration of the fetus. The limit between the two is arbitrarily established, with the demarcation being established at 32-34 weeks of pregnancy, according to the moment of the diagnosis[8]. Evidence suggests that the main cause for both types is represented by placental insufficiency. Up to 50% of the early-onset growth restriction is accompanied also by preeclampsia and abnormal Doppler on the uterine arteries whereas late-onset growth restriction is associated with preeclampsia in under 10% of the cases[9-12]. Ultrasound imaging is a non-invasive method used to evaluate the fetal development[9-12].

In order for a pregnancy to develop properly, first it needs to have a successful placental implantation and development through the trophoblastic invasion process, either ways utero-placental insufficiency may appear; placenta is the main factor that will influence the birthweight[13,14]. In the first mentioned type of IUGR, early-onset, the placental hypo-perfusion, that appears due to an abnormal process of vascular

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remodeling and endothelial cell dysfunction may finally lead to utero-placental thrombosis. Through ultrasound examination this process can be monitored by Doppler study of the umbilical artery and ductus venosus, helping the obstetrician to evaluate and decide for the proper time of delivery[11,15].

Thrombophilia, either inherited or acquired, is listed in the literature as a risk factor for placental vascular disorders and the presence of secondary thrombosis with hypercoagulability which could lead to impairment of matero-fetal perfusion[16]. In the Caucasian population, the frequency for Factor V Leiden (FVL) is about 1% to 15%, according to different studies, for heterozygous mutation and less than 1% for the homozygous one[17]. MTHFR is found in about 5-15% for homozygous state and in almost half of the population for the heterozygous type; regarding the prothrombin gene mutation G20210A, it is found in about 2% to 7% of the population[18]. The prevalence of thrombophilic mutations dependent on race and ethnicity as in East Asia for example, Protein C and Protein S deficiencies are much more prevalent than MTHFR, prothrombin, or FVL mutations[19,20]. The role of these mutations as risk factors for IUGR is still not very well known. Besides, routine screening for thrombophilic mutations is not considered cost-efficient, as their prevalence is relatively low, and due to ongoing controversial results cited in medical literature.

Methods

In this study we aimed to compare the prevalence of thrombophilia in IUGR cases, not including the ones determined by chromosome disorders, congenital anomalies or infections and to test the association between the two. As IUGR and inherited thrombophilia are both relatively rare cases, in our clinic, we only encountered 29 patients to match our criteria.

This study was conducted at the Obstetrics and Gynecology Clinic of the Bucharest University Emergency Hospital, Romania which included 343 female pregnant patients, during a period of one year, from October 2015 to October 2016. All fetuses were without signs of congenital infections, chromosomal abnormalities or malformations. The patients included in the study presented with singleton pregnancy of 20 week of gestation or greater. The patients were distributed in two groups, one comprising patients with no clinical or ultrasonographical signs of IUGR, with birth weight above the 10th percentile for gestational age and sex, consisting of 314 patients, and the other, consisting of 29 patients with IUGR, with birth weight below the 10th percentile for gestational age and sex, subdivided in other two smaller groups, one from 20 weeks of gestations to 31 week and 6 days, at the moment of examinations and the other consisting of patients from 32 weeks of gestation to term. We performed tests for inherited thrombophilia: FVL mutation (G1691A) and Factor V H1299R, Prothrombin G20210A mutation, MTHFR C677T and A1298C genotype, Factor XIII, plasminogen activator inhibitor 1 (PAI-1) gene mutation and endothelial protein C receptor. Data regarding personal or family history of venous thromboembolism, age, obesity, smoking, and obstetrical risk factors such as recurrent pregnancy loss, previous pregnancies with placental abruption, preterm birth, or pre-eclampsia were collected. Data collected from patients were introduced in a database

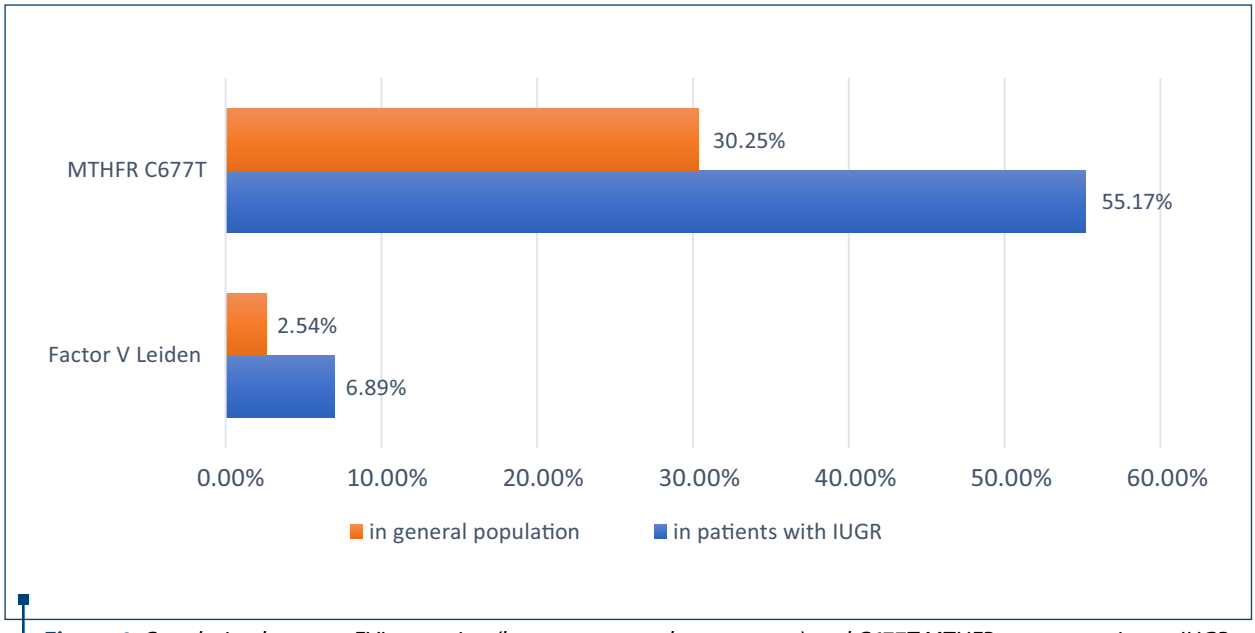

Figure 1. *Correlation between FVL mutation (heterozygous or homozygous) and C677T MTHFR gene mutation to IUGR showing a greater proportion of fetuses with IUGR in patients affected by thrombophilia*

Table 1 Prevalence of inherited thrombophilia in studied group

Factor	Mutation site	Number of cases	Percentage (total)
Factor V G1691A	GA heterozygous	2	6.89 %
Factor V H1299R	AG heterozygous CT homozygous	4 0	13.79%
Prothrombin G20210A	GA heterozygous AA homozygous	0 0	0%
MTHFR C677T	CT heterozygous TT homozygous CC homozygous	12 3 1	55.17%
MTHFR A1298C	AC heterozygous CC homozygous	6 1	24.13%
Factor XIII	GT heterozygous TT homozygous	8 1	31.03%
PAI-1, polymorphism 4G/5G	4G/5G heterozygous 5G/5G homozygous 4G homozygous	5 1 4	34.48%

in Excel, and further statistically analyzed using T-test, aimed to investigate the relationship between risk factors (ie thrombophilic mutations) and IUGR, where $p<0.05$ was statistically significant.

Results

In our group of 343 pregnant women we studied the association between IUGR and presence of hereditary thrombophilia and concluded that 29 pregnant women (8.45%) were diagnosed with IUGR by fetal Doppler ultrasound. We found a positive association between FVL mutation (heterozygous or homozygous), respectively C677T MTHFR gene mutation and IUGR. About 6.89 % of the patients in the second group presented with FVL mutation, comparing to only 2.54% in the first group, being 2 to 3 times more prevalent in the fetuses affected by IUGR. Similarly, 55.17% of the patients in the second group presented with MTHFR C677T genotype comparing to 30.25% in the first group (Figure 1). For the remaining types of thrombophilia, the difference was not significant or relevant. About 14 of the 29 patients from IUGR

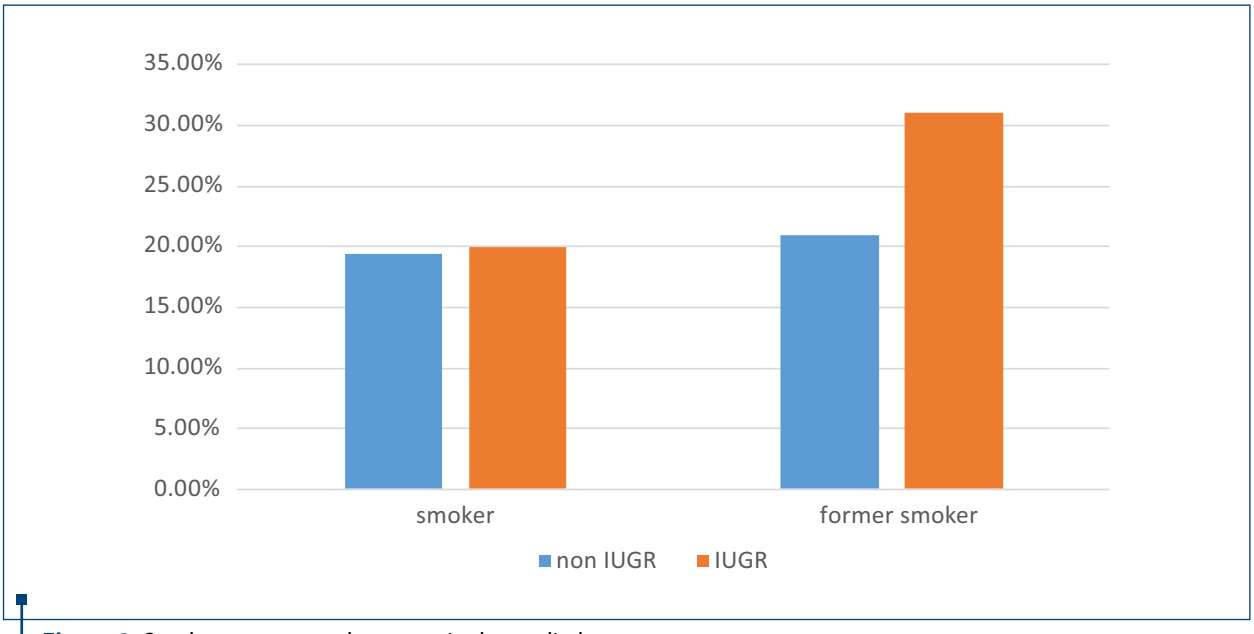

Figure 2. *Smoker vs. non-smoker status in the studied group*

group presented at 20 to 32 weeks of pregnancy (early onset growth restriction), whereas 15 presented with late onset growth restriction.

Mutation for the FVL was found in 6.89% (n=2) of the patients with IUGR, as compared with 13.79% (n=4) of the women for FV H1299R. We did not encountered any case of Prothrombin G20210A mutation in the IUGR group, this, may be noted, could be due no small number of cases. About 55.17% (n=16) cases for MTHFR C677T vs 24.13% (n=7), for MTHFR A1298C. For Factor XIII 31.03% (n=9) and for PAI-1 34.48% (n=10) (Table 1).

From their personal medical history, in the IUGR group, 6 patients have had a spontaneous abortion in the first trimester, and one patient presented with stillbirth at 34 weeks of pregnancy. From their family medical history, 27.58% (n=8) patients presented with stroke at a young age, hypertensive disorders or cardiac disease.

There are no major differences between the smoker or non-smoker status in the studied group. About 61 patients from the non-affected by IUGR fetuses declared that they were active smokers, representing 19.42%, similar to the IUGR group where 20.68% (n=9) were smoking. Regarding the former smoker status, the percentage was also similar: 21.01% (n=66) vs 31.03% (n=9) (Figure 2).

Even though there were no pathognomonic placental lesions for thrombophilia, we observed some modifications that may indicate maternal thrombotic disease such as increased placental calcifications or venous lakes, that are more severe as they appear earlier. Also, we can observe modification in placental weight, infarcts or atherosis (Figure 3).

Discussion

When affected by IUGR the fetus does not reach its biological growth potential as a consequence of impaired placental function. Doppler ultrasonography can assess both uteroplacental and fetoplacental blood flow velocities and shows hemodynamic redistribution as a response to fetal adaptations to the distress environment, as an indirect sign of placental damage[2]. Even though in a smaller proportion of the total cases, as earlier it appears during pregnancy, the worse the damage is for the IUGR affected fetuses and

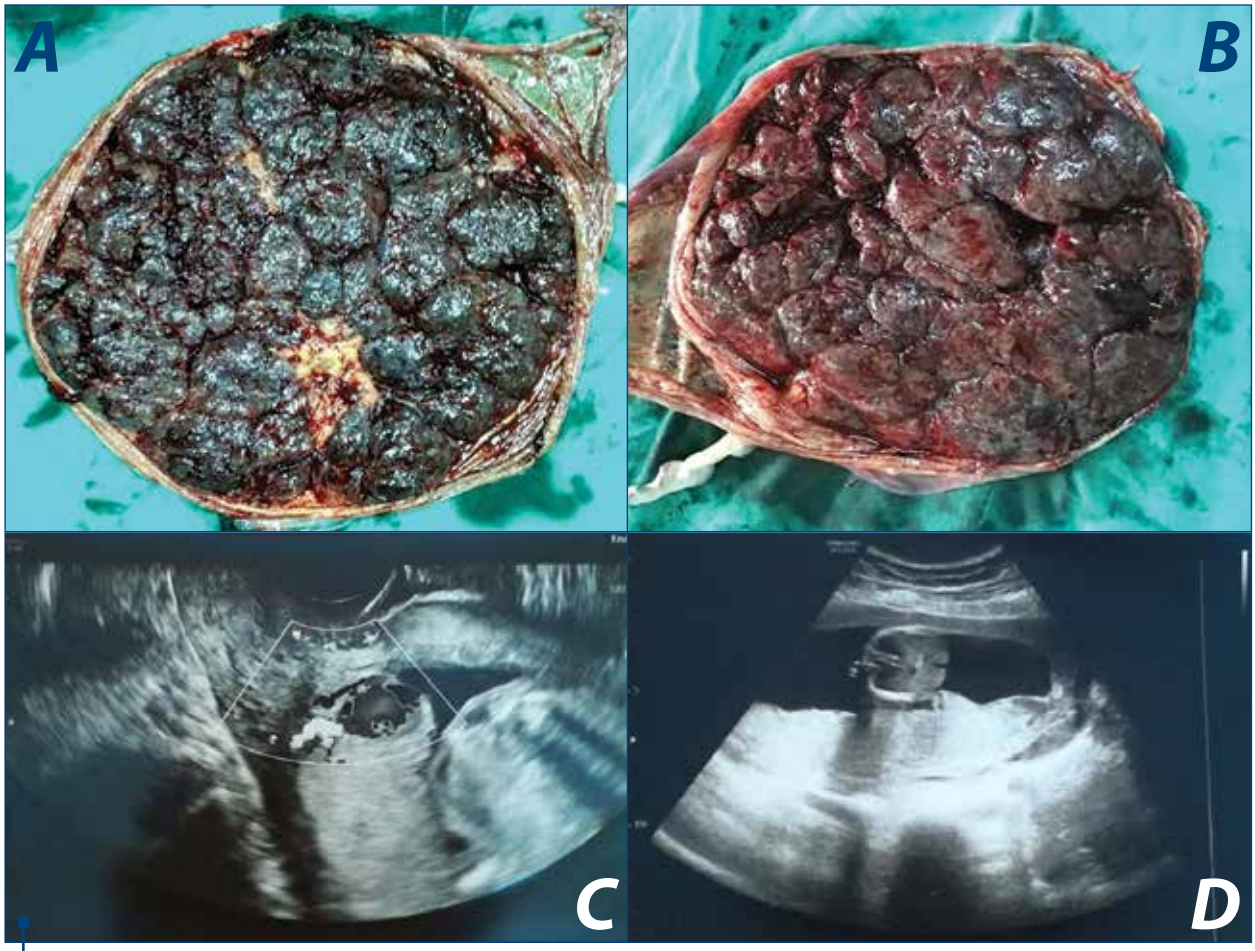

Figure 3. *Macroscopic (A and B) up – calcifications and atherosis and ultrasonographic (C and D) down – venous lakes placental images from patients with thrombophilia*

in the same time it reveals a more severe placental insufficiency[2,11]. The separation from a constitutionally small for gestational age fetus is important to be made, even though this may be more difficult as not all the patients monitor their pregnancy according to the medical advice. Either they register late for the first prenatal consultation, or they do not keep up with the recommended medical checkups. In general, hemodynamic redistribution evaluated by Doppler ultrasound evaluated through cerebroplacentar ratio, uterine artery Doppler and ductus venosus and an estimated weight below the 10th percentile will indicate chronic fetal distress and intrauterine growth restriction[2].

According to increasing available evidence, thrombophilia is not responsible only for pregnancy associated thromboembolism, but could also be responsible for other vascular complications of pregnancy being some of the most important obstetrical complications, starting from IUGR, preeclampsia/eclampsia, placental abruption, recurrent miscarriages or unexplained stillbirth. There are some studies that shows the causality between women affected by thrombophilia and the risk for developing IUGR[21,22]. One of the most recent ones, highlighted the connections between PAI-1 and MTHFR thrombophilic mutations and fetuses affected by IUGR[23,24], as well as for the Prothrombin 20210 homozygous mutation and FVL homozygous genotype, even though for the last two with a lower statistical significance[23], while other are still researching and focusing mainly for the last two mentioned, as they are known to be more thrombogenic[25].

Some authors also found an association between fetal growth restriction and the presence of inherited thrombophilia[20,26]. Regarding the relation between ATIII deficiency and IUGR, although rare, a positive correlation was also found, and it was considered an additional cause for intrauterine growth retardation[27].

In an extensive research of various medical platforms a correlation was made between small for gestational age and mothers with FVL mutation[28], while the presence of MTHFR in homozygous state presented, as mentioned in other studies, with a high risk for IUGR, results in concordance with our study. MTHFR mutation along with FVL and prothrombin all have a negative influence for adverse pregnancy outcome regarding preeclampsia, IUGR and placental abruption[24].

Livrinova et al. found a higher prevalence for MTHFR homozygous and heterozygous, Prothrombin heterozygous and FVL heterozygous in the group with IUGR fetuses[24].

There are no particular placental lesion pathognomonic for thrombophilia, but some modifications that may indicate maternal thrombotic disease include increased placental calcifications and multiple venous lakes, especially if seen early in pregnancy, modification in placental weight, also small for the given gestational age, infarcts, or atherosis[29].

Considering the data mentioned above, pregnant patients should undergo tests for inherited thrombophilias when IUGR is present. When severe IUGR appears, testing for the mentioned mutations is also recommended by prestigious associations as The American College of Obstetrics and Gynecology[30].

Conclusions

Fetuses with iugr are at risk for perinatal morbidity and mortality and with short and long-term health consequences. The impact of inherited thrombophilia in pregnancy is investigated from many authors and in ours study data showed a positive correlation between FVL mutation and C677T MTHFR gene mutation and IUGR being up to 3 times more prevalent in the fetuses affected by IUGR. The management of these cases is challenging and one of the main purposes is achieving the best balance between the risks of leaving the fetus in utero versus the complications of prematurity. Understanding the process of IUGR is indispensable for developing effective therapeutic strategies. ■

Conflict of interests: The authors declare no conflict of interests.

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