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THE ASSOCIATION BETWEEN INTRAUTERINE GROWTH RETARDATION AND MATERNAL THROMBOPHILIA

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Nart Faruk Kuneshko ✉, ***Vasilina Golomazova***, ***Olga Pitirimova***

[1] *Faculty of Obstetrics and Gynecology, Sklifosovsky Research Institute, Moscow;*
[2] *Faculty of Obstetrics and Gynecology, Sechenov First Moscow State Medical University, Moscow;*
[3] *National Scientific and Practical Center of Cardiovascular Surgery, Moscow, Russia*

✉ *drnartfaruk@mail.ru*

ABSTRACT — Intrauterine growth retardation (IUGR) contributes to fetal morbidity and mortality, but its etiology is unknown in most cases. Our aim was to indicate the association between thrombophilia (genetic and acquired) and IUGR. A case-control study of 185 pregnant women with compensated and decompensated forms of placental insufficiency and IUGR has been conducted, with a control group (n=50) consisted of women who had normal growth fetuses. This case-controlled study demonstrated significantly higher prevalence of genetic and acquired thrombophilia in women with IUGR compared to women with normal pregnancies. However, further studies which employ randomized controlled trials and determine the preventive effect of the administration of LMWH (Low-molecular-weight heparin) and/or low-dose aspirin on women in risk groups for thrombophilia are required for a establishing a definitive relationship. Pregnant women with genetic or acquired thrombophilia belong to a high-risk group for the onset of intrauterine grown restriction syndrome. Our study included a small number of patients. To evaluate a more accurate relationship it is required to perform randomized controlled trials and determine potential benefits of administration of LMWH and/or low-dose aspirin in order to provide prophylaxis of IUGR in risk groups with genetic and acquired thrombophilia.

KEYWORDS — IUGR, FGR, FWA, thrombophilia, placental insufficiency, case-control, hemotrophic phase.

ABBREVIATIONS AND ACRONYMS:

IUGR — Intrauterine growth retardation
LMWH — Low-molecular-weight heparin
FGR — Fetal growth retardation
FWA — Fetal weight gain
HC — Head circumference
BPD — Biparietal head size
FAC — Fetometric abdominal circumference
FL — Femur length
FMP — Fetal movement profile
SGA — Small-for-gestational age

INTRODUCTION

Fetal growth retardation (FGR) is a term that describes a pathologically small fetus that has not reached its growth potential and has a high risk of perinatal complications (a slowed anticipated fetal weight gain (FWA) and/or abdominal circumference (AUC) <10th percentile, combined with abnormal blood flow as measured by US Doppler or FWA values <3rd percentile).

Causes leading to the development of PPH can be divided into 4 groups: maternal, placental, fetal and genetic. Although their pathophysiology is different, they all ultimately lead to the same result: decreased uterine-placental perfusion and fetal nutrition.

Fetal growth (fetal physical development) is a dynamic process and its evaluation requires multiple observations of fetal size throughout pregnancy. Fetal size is determined by measuring the head circumference (HC), biparietal head size (BPD), FAC (fetometric abdominal circumference), femur length (FL), and/or FMP (fetal movement profile) calculated by various formulas during ultrasound. These CRs use the terminology to describe fetal growth/developmental abnormalities shown in Table 1. Identification of FGR is often difficult because fetal growth cannot be assessed by a single measurement of fetal size and growth potential is a hypothetical concept.

Despite low sensitivity and specificity, the determination of growth-mass indices and uterine floor height (UFH) are the only routinely available physical examination methods. The UFH should be measured and entered into individual charts, or gravidograms; suboptimal fetal growth should be diagnosed by applying the MacDonald rule when the uterine floor height is less than ≥3 cm of gestational age in weeks.

It is recommended to conduct UFN measurement starting from 22nd week of gestation to detect fatal growth deficiencies.

Intrauterine growth retardation (IUGR), which is also referred to as fetal growth retardation (FGR) in medical literature, is a term which describes a condition in which a fetus experiences reduced growth compared to the expected rate. A widely used definition suggests that IUGR is present when the weight of a fetus lies below the 10th percentile for its gestational age; however, other parameters should be also em-

ployed to differentiate between IUGR and small-for-gestational age (SGA) condition.

IUGR contributes to fetal morbidity and mortality and is associated with higher chances of premature conditions and certain non-communicable diseases in adulthood, but its etiology is unknown in most cases.

Studies suggest such causes of IUGR as certain chronic and infectious diseases in mothers (diabetes, cardiovascular disease, etc), genetic disorders, placental insufficiencies, abnormal placentation, malnutrition and others. Our aim was to indicate the association between thrombophilia (genetic and acquired) and IUGR.

METHODS

As the main method of this study, we selected a case-control study of 185 pregnant women with compensated and decompensated forms of placental insufficiency and IUGR with a control group of women (n=50) who had normal growth fetuses. All women were tested in the third trimester for the following parameters: factor V Leiden, prothrombin gene (G20210A), MTHFR (C677T) and PAI-1 polymorphism and circulation of APA (LA, Cardiolipin Antibodies, Beta-2 Glycoprotein I Antibodies, Prothrombin Antibodies). We then compared the occurrence of IUGR

RESULTS

There were discovered no significant associations between mutations in prothrombin gene G2021A (0.16 percent points difference of occurrence between case group and control group for homozygote pattern and 1.03 percent points difference for heterozygote pattern) and Factor V Leiden thrombophilias (1.08 percent points difference for homozygote and about 0.5 percent points difference for heterozygote patterns) and IUGR in either of the groups.

Strongly significantly higher odds for IUGR are present in patients with PAI, MTHFR gene mutation (heterozygote and homozygote pattern) and circulation of antiphospholipid antibodies (Table 2). Patients with IUGR were found to be almost 4 times more likely to have plasminogen activator inhibitor caused thrombophilia than patients with normal pregnancies. MTHFR gene mutation caused thrombophilia chances are more than two times higher for women with IUGR (2.3 times higher for both homozygote and heterozygote pattern). The difference of occurence thrombophilia caused by circulation of aPL antibodies in patients with IUGR differs from 3.9 times higher chances for cardiolipin antibodies to 7.3 times higher prothrombin antibodies.

We also discovered a higher occurrence of multigenic (5.5 times more often) and combined (7.7 times more often) thrombophilias in women with IUGR.

DISCUSSION

This case-controlled study demonstrated significantly higher prevalence of genetic and acquired thrombophilia in women with IUGR compared to women with normal pregnancies. Furthermore, strongly significant associations between PAI and MTHFR thrombophilias and IUGR are demonstrated. The associations between IUGR and circulation of aPL antibodies differ for different antibodies type; however, it is, in principle, significantly high. Our study showed a higher prevalence of multigenic (33%) and combined thrombophilia (30,8%) in IUGR pregnancies compared with 6% and 4% in the control group. The association between IUGR and FV Leiden and Prothrombin gene G20210A mutations are controversial: no significant difference in occurrence o these phenomena has been found between case group and control group.

CONSLUSION

Our study suggests an association between genetic and acquired thrombophilias in pregnant women and intrauterine growth retardation. However, the occurrence of different variations of thrombophilia in women with IUGR is not heterogenous.

The key role of thrombophilia in the pathogenesis of obstetric complications is as follows: microthrombosis of the vessels of the placental bed and, accordingly, a violation of uteroplacental blood flow occur. Implantation, invasion of trophoblast in the presence of genetic defects of coagulation is disrupted. It should be noted that in thrombophilia not only the early (avascular) implantation phase, but also the later stages of implantation (hemotrophic phase) and placentation suffer. Antiphospholipid antibodies are able to disrupt the process of trophoblast differentiation, which is manifested in changes in the embryo's adhesiveness, syncytium fusion disturbance, the depth of trophoblast invasion, a decrease in the production of chorionic gonadotropic hormone, and an increase in thrombotic tendencies. All of the above trends contribute significantly to the development of IUGR. Thus, pregnant women with genetic or acquired thrombophilia belong to a high-risk group for the onset of intrauterine grown restriction syndrome.

Our study included a small number of patients. To evaluate a more accurate relationship it is required to perform randomized controlled trials and determine potential benefits of administration of LMWH and/or low-dose aspirin in order to provide prophylaxis of IUGR in risk groups with genetic and acquired thrombophilia.

Table 1. *(IUGR)*

Title	Define
IUGR	Slow anticipated fetal weight gain (FWG) and/or abdominal circumference gain (ACG) or FWG and/or ACG values < 10th percentile combined with abnormal blood flow as measured by ultrasound Doppler; or FWG and/or ACG values < 3rd percentile
Congenital IUGR	Estimated fetal weight is less < 3rd percentile

Table 2. *Prevalence of thrombophilia in the two groups*

Factor	Cases (n=185)		Control (n=50)	
FV Leiden homozyg	2	1,08%	0	0,00%
FV Leiden heterozyg	12	6,49%	3	6,00
Prothrombin homozyg	4	2,16%	1	2,00%
Prothrombin heterozyg	13	7,03%	3	6,00
MTHFR homozyg	17	9,19%	2	4,00
MTHFR heterozyg	51	27,57%	6	12,00
PAI	64	34,59%	4	8,00
Multigenic	61	32,97%	3	6,00
LA	21	11,35%	1	2,00
Cardiolopin AB	43	23,24%	3	6,00
B2Gpla AB	72	38,92%	4	8,00
Prothrombin AB	54	29,19%	2	4,00
Combined thrombophilia	57	30,81%	2	4,00

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