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CLINICAL ARTICLE

Genetic thrombophilias and uterine artery Doppler velocimetry and preeclampsia

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Abstract

Objective: The aim of this study was to evaluate the correlation between genetic thrombophilic mutations, uterine artery Doppler at 24 weeks of gestation and preeclampsia. *Methods:* In a case control study we performed the genetic analysis for Leiden mutation of factor V gene (FV), G20210A mutation of the prothrombin gene (PT) and C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene in 103 women that had already attended routine ultrasonography scanner at 20 weeks at our Department. *Results:* The frequency of heterozygous carriers of the factor V Leiden was 17.4% in the women with preeclampsia and abnormal artery Doppler compared with 3.12% in the patients with normal pregnancies. This difference was statistically significant ($P<0.05$). The frequency of mutation G20210A of prothrombin gene was 1.5 vs. 4.3% between women with normal pregnancies and with preeclampsia. This difference is not statistically significant. The frequency of homozygous patients for the C677T mutation of MTHFR gene among the patients with preeclampsia was 21.7% and in the control group was 10.3%, but this difference is not statistically significant. No thrombophilic gene variants were found in women with preeclampsia and normal uterine artery Doppler. *Conclusion:* We demonstrated the important association between factor V Leiden mutation, abnormal uterine Doppler at 24 weeks and preeclampsia in our population.

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1. Introduction

Hypertensive disorders occur in 5—15% of pregnancies and are one of the major causes of maternal and fetal morbidity and mortality [1]. Being able to predict which patients are at risk for the development of preeclampsia would be of great value to discriminate the population that could benefit from more aggressive treatment and intensive observation.

The pathogenesis of preeclampsia is still poorly understood but is thought to be related intimately to changes in the placental microcirculation [2]. Deficient placentation is characterised by inadequate trophoblast invasion into the maternal spiral arteries and failure to develop low-resistance uteroplacental circulation [3]. However, various haemodynamic and biochemical measures have been found to have limited accuracy as screening measures for preeclampsia [4]. Clinical studies of uterine artery Doppler screening are contradictory, and a recent meta-analysis has concluded that the uterine artery flow velocity waveform ratio has limited diagnostic prediction for preeclampsia [5].

Abnormal placentation is also associated with an increased tendency toward thrombosis.

This complication might be the result of the combination of one acquired risk factor (pregnancy) with genetic thrombophilic mutations [6,7].

The aim of this study was to evaluate the clinical usefulness of screening of genetic thrombophilic mutations and uterine artery Doppler at 24 weeks of gestation in the prediction of preeclampsia in low-risk pregnant women.

2. Material and methods

In a case control study, between February and July 2003, was studied 39 pregnant women with preeclampsia and 64 normal pregnant controls admitted at the Department of Obstetric and Gynecology, University of Udine, Italy. The controls were identified as women that had already attended routine ultrasonography scanner at 20 weeks at our Department and without risk factors. Outcomes were defined as preeclampsia using the criteria of American College of Obstetricians and Gynecologists [8]. Women with chronic hypertension, diabetes, previous fetal death, intrauterine growth retardation, multifetal gestations, hydrops fetalis, preeclampsia in a previous pregnancy, vascular and connective tissue disease, nephropathy, antiphospholipid antibody syndrome, obesity and African—Italian race. All subjects were negative for lupus anticoagulant and anticardiolipin antibodies. All the patients used folic acid all along pregnancy. These patients did not receive aspirin or anticoagulant therapy and no women had a family or personal history of thromboembolic disease.

The genetic analysis was performed for Leiden mutation of factor V gene (FV), G20210A mutation of the prothrombin gene(PT) and C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene in all 103 women that had already attended routine ultrasonography scanner at 20 weeks at our Department. They had color Doppler examination of the uterine arteries integral part of 20 weeks scanning (Acuson Sequoia, Acuson, Mountain View, CA). The right and left uterine arteries were identified at the apparent crossover with the external iliac arteries, and pulsed-wave Doppler was used to obtain waveforms. When three similar consecutive waveforms were obtained, the resistance index (RI) was calculated from each uterine artery and the presence or absence of a notch was determined. An RI of >0.58 was defined as abnormal. In each subject the placental position was also recorded. Doppler findings were recorded in a computer patient database and thermal waveforms images were retained. The whole procedure took an average of 6 (range 3—12) min.

Women with abnormal Doppler results were examined again at 24 weeks gestation and those with persistently abnormal results were followed closely. Routine fetal biometry measurements were obtained followed by color Doppler examination of the arteries every 4 weeks. Women with normal uterine artery Doppler received routine antenatal care.

The ethics committee of faculties of Medicine of the University of Udine approved this study. Written informed consent was obtained in each case before the study begun.

The presence of Factor V Leiden, mutation G20210A of prothrombin (PT) gene and C677T of methylenetetrahydrofolate reductase (MTHFR) was evaluated by PCR procedures.

Oligonucleotides used as primers were: 5′-CATACTACAGTGACGTGGAC-3′and 5′-TGTTC-TCTTGAAGGAAATGC-3′ for FV Leiden [9]; 5′-TCTAGAAACAGTTGCCTGGC3′ and 5′-ATAGCACTGG-GAGCATTGAAGC-3′ for the mutation G20210A of PT gene [10]; 5′-AGGGAGCTTTGAGGCTGACCTGAA-3′ e 5′-ACGATGGGGCAAGTGATGCCCATG-3′ for the C677T mutation of the MTHFR gene [11].

The PCR parameters were the following:

FV Leiden: denaturation 95°, 30″; annealing 58° 60″; elongation 72° 60″; 35 cycles.