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The Association of Endothelial Nitric Oxide Synthase Gene Polymorphisms and Preeclampsia Susceptibility

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Preeclampsia (PE) is a pregnancy specific syndrome that can affect every organ system and is a major cause of maternal and perinatal morbidity and mortality worldwide. The PE affects 0.4-2.8% of all pregnancies in developed countries, while its incidence is higher in developing countries (1). Although PE is much more than gestational hypertension with proteinuria, existence of proteinuria itself is an important diagnostic criterion. Hypertension is defined as a systolic blood pressure (SBP) value $\geq$ 140 mm Hg or a diastolic blood pressure (DBP) $\geq$ 90 mm Hg recorded for the first time after midpregnancy. Preeclampsia is diagnosed when hypertension and one of the following criteria are present: proteinuria ($\geq$ 300 mg/24 h) or a urine protein-to-creatinine ratio $\geq$ 0.3, or dipstick 1 + persistent proteinuria, thrombocytopenia (PLT $<$ 100000/μL), kidney insufficiency (creatinine $>$ 1.1 mg/dL or doubling of baseline), liver involvement (serum transaminases level $\geq$ twice normal), cerebral symptoms (headache, visual disturbances, convulsions), pulmonary edema. Hypertension attributable to pregnancy should resolve within 12 weeks after delivery (2). In addition, neonatal complications of Preeclampsia include prematurity, fetal growth restriction, neurologic damage (hypoxia related) and perinatal death. Based on the gestational age, PE can be classified into early onset PE (EOPE), in which the diagnostic criteria develops before 34 weeks of gestation, and late onset PE (LOPE), which develops after 34 weeks of gestation. On the other hand, based on the severity of the condition, PE is classified as severe or mild (1).

Available literature on this subject describes two stages for this disorder. Stage 1 is characterized by faulty endovascular trophoblastic remodeling of uterine arteries. However, stage 2 is related to the release of placental factors into the maternal circulation, which results systemic inflammatory response and endothelial activation (3). The progression of PE is rapid, beginning with the impairment of vascular refractoriness to vasoactive agents, followed by vasoconstriction, which causes the decrease in intravascular volume. Preeclamptic changes begin with endothelial damage and leakage of plasma constituents into vessel walls (4).

Despite numerous and extensive analyses and observations which have been performed on animal models and human studies during the last hundreds of years, the exact pathophysiology of PE is still unclear. However, there is no doubt that endothelial dysfunction is one of the basic mechanisms which is associated with PE occurrence (5). Endothelial dysfunction, as a syndrome, is defined as the absence of antithrombotic, angiogenic, inflammatory and vasodilator functions of endothelium. Evidences from documented cases have revealed that the bioactivity or bioavailability of nitric oxide (NO) is reduced in this condition, and, in turn, vasodilator capacity and vascular protection against harmful agents is impaired. The NO is a powerful endogenous vasodilator, which performs key roles in blood pressure regulation, vascular dilation, vascular smooth-muscle proliferation and inhibition of platelet aggregation. These abilities recommend this molecule as an attractive candidate for predisposition to PE (6).

Nitric oxide (NO) is synthesized from L-arginine and molecular oxygen by a family of three enzymes called NO synthases (NOS): NOS1, NOS2, and NOS3. The constitutive endothelial NOS (eNOS or NOS3) is expressed in the endothelium, and is encoded by a 26 exons gene which is located on chromosome 7q36, with a total size of 21 kb. This bases sequence encodes a 4052 nucleotides large mRNA (7). Since NO cannot be stored, its production is controlled through the regulation of expression or activity of the eNOS enzyme. In general, the NOS3 gene has been reported to act as a 'susceptibility gene' in various

vascular diseases. Different single nucleotide polymorphisms have been described in the promoter, exons and introns of the eNOS gene, while three of them have received an increased research interest. 1- The Glu298Asp (G894T, rs1799983) polymorphism in exon8 leads to amino acid change, which could alter the protein-protein interaction of a mutant enzyme with caveolar protein1 (8). 2- T-786C polymorphism (rs2070744) in the promoter region of the gene which reduces promoter activity (9). 3- A 27 bp variable number of tandem repeat (VNTR) in intron 4 (4ab, rs61722009) polymorphism. It is probable that the polymorphism is in linkage disequilibrium with other functional variants in regulatory regions of the NOS3 gene (10).

There are several reports about the association between eNOS gene polymorphisms and PE susceptibility, with controversial results. Recently, we have conducted a case control study about the association between eNOSGlu-298Asp polymorphism and PE susceptibility and we have concluded that Glu/Asp and Asp/Asp genotypes are independent risk factors for PE development (11). Our results were consistent with results obtained by researches in the United States (12), while there were in contrast with results of a trial performed in the United Kingdom (13). However, the results of a meta-analysis refute the correlation between this polymorphism and PE (14). In another study, we performed genotype analyses on eNOS T-786C and 4ab polymorphisms in PE women and normotensive pregnant women. Although we found a higher frequency of ba genotype of 4ba and TC genotype of T-786C polymorphisms, the differences were not statistically significant (15). However the results of a recent meta-analysis revealed that the eNOS gene T-786C and 4b/a polymorphisms were significant contributors to the PE risk, especially for European individuals (14).

Because ethnicity plays an important role in complex genetic diseases such as PE, these different results are common and similar studies are necessary (especially on placenta) to determine the exact effects of these polymorphisms and PE susceptibility.

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