

The role of angiotensin converting enzyme (ACE) gene polymorphisms in pregnancy complications.

Pregnancies require an even balance of coagulation and fibrinolysis in order to avoid excess fibrin accumulation in placental vessels and intervillous spaces as well as to secure fibrin polymerization and stabilization of the placental basal plate. Adequate fine-tuning of fibrinolysis is mandatory in order to prevent hemorrhage and hence minimal alterations in the fibrinolysis cascade leading to either hypo- or hyperfibrinolysis are suspected to interfere with placentation and early pregnancy. Hence genes regulating the vascular tone may serve as vital etiological factors. The 'physiological remodeling' of spiral arteries throughout pregnancy is mediated by the renin-angiotensin system (RAS), which is one of the main factors regulating blood pressure, fluid and electrolyte balance. Angiotensin converting enzyme (ACE) encoded by the ACE gene, is a key component of the Renin Angiotensin system mediating the conversion of angiotensin I to angiotensin II. *In vitro* and *in vivo* studies indicate that ACE interferes with hemostasis through different mechanisms, including an influence on fibrinolysis, platelet aggregation and blood clotting.

Though the human ACE gene contains a number of variable polymorphic regions that can be of potential use in genetic analysis of populations, the insertion/ deletion (I/D) polymorphism in **intron 16**, has been extensively investigated. During pregnancy, marked changes in hemostasis take place and ACE D/D genotype has been proposed as a new thrombophilic factor influencing pregnancy negative events. In addition to the well-known vasomotor functions, renin-angiotensin system is also involved in key events of the inflammatory process by increasing vascular permeability and contributing to the recruitment of inflammatory cells. Regarding hemostasis, several reactions are modulated by the renin-angiotensin system, and evidence exists for an association between the ACE D/D genotype and increased risk of thrombotic events. Moreover, ACE by bradykinin degradation reduces nitric oxide levels, therefore contributing to endothelial dysfunction. *J. Obstet. Gynaecol. Res. Vol. 34, No. 3: 301–306, June 2008*

The renin–angiotensin system (RAS) has been shown to be involved from early stages of fetal/placental development. Expression of angiotensinogen, renin, angiotensin converting enzyme and angiotensinogen II type 1 receptor (AT1) has been demonstrated in first trimester deciduas and in and around the spiral arteries, which may influence vascular remodeling of the spiral arteries. Failure of physiologic transformation of the spiral arteries has been demonstrated in women undergoing preterm labor with or without intact membranes. ACE activity has been shown to be higher in preterm infants. ACE as a component of the RAS converts angiotensin I to angiotensin II which acts as a potent vasoconstrictor and also as a growth factor resulting in medial hyperplasia of the blood vessels. The DD genotype with its

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higher ACE activity has been shown to be a risk factor in pregnancies complicated by preeclampsia, intrauterine growth restriction and recurrent pregnancy loss, all of which have a common factor of defective placentation. Hence it is plausible to suggest that ACE/RAS abnormalities, manifesting as abnormal vascularisation of the placenta may be partly responsible for precipitating preterm labor among other placenta related complication. R. Uma et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology, 2008

The ACE (I/D) polymorphism is characterized by the presence (insertion (I) or deletion (D)) of a 287-bp fragment and has been identified in intron 16 of this gene. ACE is primarily localized in venous endothelial cells of stem villous tissue in the placenta, and ACE activity, ACE protein expression, and ACE mRNA expression are higher in pre-eclamptic placenta than in placenta from uncomplicated pregnancy. Venous endothelial cells within placental tissue and umbilicus play an important role in the regulation of feto-placental RAS, and in response to hypoxic conditions, such as preeclampsia, the feto-placental unit induces ACE activity in the placenta. Such an effect is likely to lead to regulation of the fetal circulation. Braz J Med Biol Res 40(4) 2007

In summary, the presence of heterozygous or homozygous ACE gene polymorphism is a risk factor for the following maternal and fetal complications:

1. Hypertension in pregnancy and beyond.
2. Pre-eclampsia due to poor spiral arteriolar conversion.
3. Poor placental growth leading to fetal growth restriction.
4. Preterm birth.
5. Recurrent pregnancy loss.
6. Endothelial dysfunction and abnormal vascular wall thickening leading to poor vascular compliance and all associated and related vasculopathies (poor maternal placental vascular development and fetal thrombotic vasculopathy).