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COMMENT

Solving preeclampsia from SNP in *IGFBP-1* gene

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Though preeclampsia (PE) is known to be one of the major causes of maternal, fetal, and neonatal mortality and morbidity worldwide, no effective therapeutic approaches that attenuate the progression of PE have been established. Once it develops, termination would be the only choice and therefore, identification of predictive tools and preventive agents is warranted in order to monitor patients closely and minimize the occurrence of adverse complications.

Shallow placentation as a result of failure in trophoblast invasion in maternal-fetal interface, is thought to be an initiating factor contributing to the development of PE. Normal course of trophoblast invasion and the development of villous tree, in turn, are regulated by a convoluted system of interactions between numerous growth factors, their receptors, and specific transmitter proteins.

Insulin-like growth factor-binding proteins (IGFBPs) are involved in modulating the effects of the insulin-like growth factors (IGFs) which have key roles in growth and apoptosis, metabolism and development. IGFBP-1, the first member of the family to be identified, is the predominant IGFBP in secretory endometrium and decidualized stromal endometrial cells, and its expression is tightly controlled. The IGF/IGFBP-1 axis is important in endometrial cyclic development and is also crucial in blastocyst implantation. *IGFBP-1* mRNA and protein are highly expressed in decidua and at the decidua-trophoblast interface in human early pregnancy. During blastocyst implantation, there may be an important interaction between decidual IGFBP-1 and trophoblast-derived IGF and involves in trophoblast invasion. However, it is unclear if the placenta-derived IGF and IGFBP-1 are secreted into the maternal or fetal circulation.

The present study by Peng et al. focused on relationships between polymorphisms of *IGFBP-1* gene and the susceptibility and severity of PE and demonstrated that women whose rs106780, one of the SNPs of the *IGFBP-1* gene, was occupied by G rather than A had a lower risk of developing PE, and a reduced risk of adverse complications [1]. IGFBP-1 level is found to be significantly elevated in maternal and fetal fluids. Maternal serum IGFBP-1 concentrations are elevated 2-fold relative to those in non-pregnant serum and are likely to be originated from both liver and decidua. Consistent with the previous studies, plasma IGFBP-1 protein levels were significantly higher in pregnant group compared with non-pregnant group in the present study. There was no significant difference in plasma IGFBP-1 concentration between the PE and non-PE groups. They have also compared the plasma IGFBP-1 levels between genotypes and found that pregnant subjects carrying AG exhibit significantly higher plasma IGFBP-1 levels than subjects carrying AA. In severe PE, maternal serum IGFBP-1 levels in the second and early third trimesters are sixfold higher, and at term are 2-fold higher, compared with normal pregnancies [2]. Another study have shown that maternal serum IGFBP-1 correlated with DBP and aspartate transcarbamylase, implying that IGFBP-1 reflects the severity of PE and liver involvement [3]. However, in the present study, Peng et al. have demonstrated that subjects whose rs106780 was occupied by G had a lower risk of developing PE, but inconsistently, they have also shown that subjects carrying G had higher levels of plasma IGFBP-1. In contrast with the previous findings, another study found decreased mid-pregnancy serum IGFBP-1 concentrations in women who developed mild PE later in gestation [4]. Vatten et al. have observed lower maternal serum IGFBP-1 levels in the first and the second trimesters in term PE women but not in preterm PE women [5]. In non-pregnant women, relatively low levels of serum IGFBP-1 have been associated with a higher prevalence of abnormal glucose tolerance and the metabolic syndrome [6]. Polycystic ovarian syndrome is

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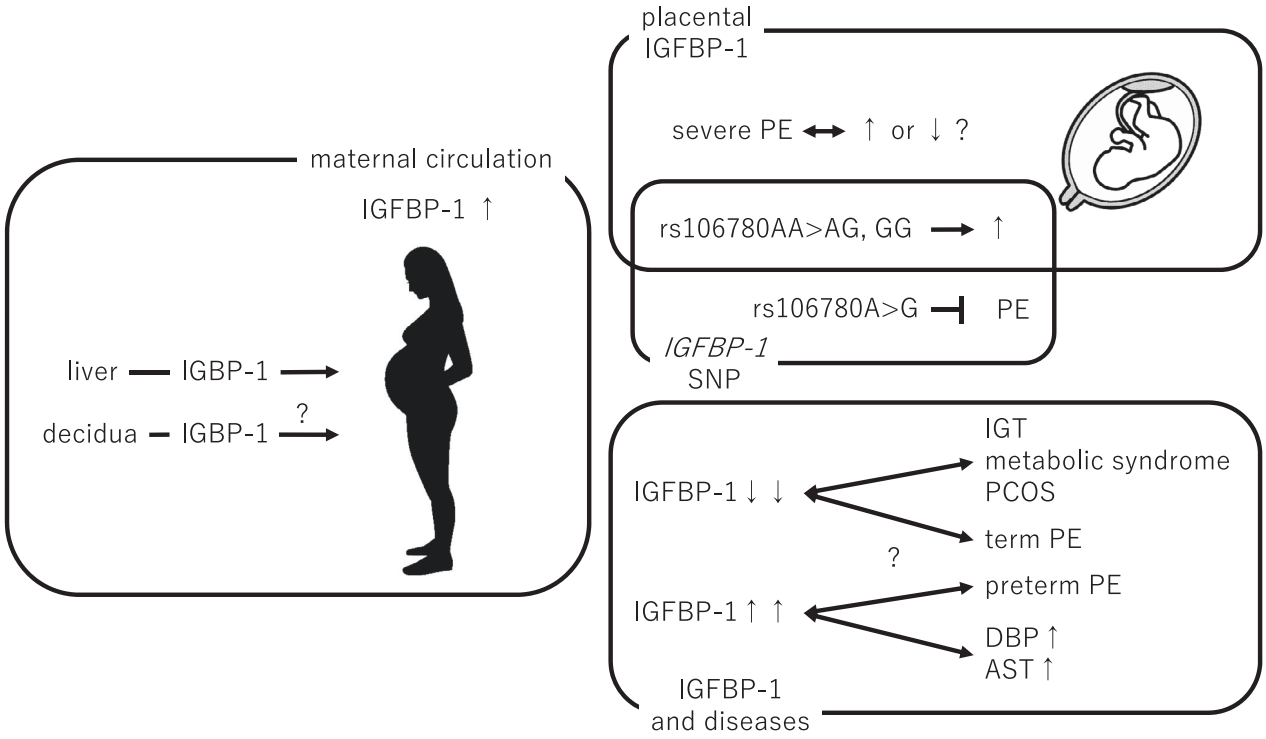
Graphical Opinion



IGFBP-1, insulin-like growth factor-binding protein; PE, preeclampsia; IGT, impaired glucose tolerance; PCOS, polycystic ovarian syndrome; DBP diastolic blood pressure; AST, aspartate transcarbamylase.

known to be associated with obesity, insulin resistance and cardiovascular risk later in life, as well as menstrual disturbance and anovulatory infertility. Low IGFBP-1 serum concentrations of IGFBP-1 occur likewise in this complex syndrome. PE diagnosed at term may reflect maternal metabolic aberrations. Therefore, this finding that low levels of serum IGFBP-1 were associated with an increased risk of term, but not preterm PE, may suggest that women with metabolic aberrations are at an increased risk of PE with onset at term. Since the previous studies have investigated that underlying pathophysiology of term and preterm PE differs, different results may have been obtained if serum IGBP-1 levels and genotypes were analyzed separately based on the time of the onset of PE.

In cycling endometrium, *IGF* gene expression is restricted to the stromal cells. *IGF-I* mRNA is expressed during the proliferative phase, whereas *IGF-II* mRNA expression predominates in secretory phase. IGF-II is also the main peptide expressed at the maternal-fetal interface in pregnancy [7]. High levels of *IGF-II* mRNA are expressed by the trophoblast especially at the invading front. In turn, mRNA encoding the IGFBP-1 is expressed at the maternal-fetal interface primarily by the decidual tissue. At the maternal-fetal interface in human pregnancy, IGF-II and IGFBP-1 appear to play and important role in paracrine interactions (Fig. 1). In addition to its regulation of IGF-II bioavailability, IGFBP-1 has IGF-independent effects, binding directly to cell membranes and altering cellular motility. IGFBP-1 contains Arg-Gly-Asp (RGD) sequence which is known to mediate recognition for several cell adhesion molecules, including the α5β1 integrin. In vitro study has demonstrated that IGFBP-1 binds, via RGD sequence, to α5β1 integrin of Chinese hamster ovary cells and stimulates their motility. Therefore, decidual IGFBP-1 may also interact directly with the invading trophoblast to regulate its activity.

In the present study, authors have also explored the association between the *IGFBP-1* gene polymorphism rs1065780 A > G and the placental tissue protein levels. No significant difference was shown in the levels of IGFBP-1 protein distribution in the PE and non-PE groups. However, in terms of genotype distribution, for the PE group, PE patients with AG or GG genotype had significantly higher IGFBP-1 protein levels compared to AA. Giudice et al. have demonstrated that concentrations of IGFBP-1 at the maternal-fetal interface have been found to be higher in cases of severe PE compared with normal pregnancies [3]. In contrast, Gratton et al. have also shown that IGFBP-1 expression was decreased significantly in severe PE placenta [8]. As previous studies have suggested that IGFBP-1

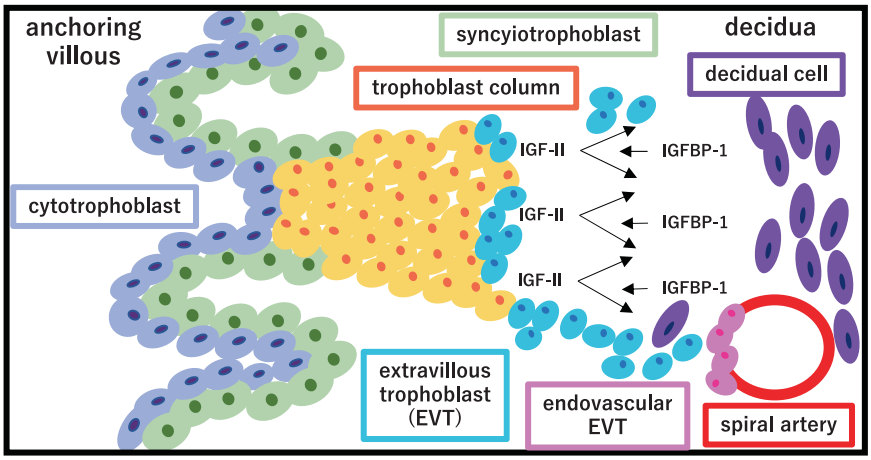


Fig. 1 Schematic representation of paracrine interaction between insulin-like growth factor II (IGF-II) and IGF-binding protein-1 (IGFBP-1) at the maternal-fetal interface

facilitates normal trophoblast invasion into the maternal decidua [7, 9], decreased IGFBP-1 expression at the maternal-fetal interface may contribute to the abnormal trophoblast invasion in PE. Previously reported increase in serum IGFBP-1 in women with severe PE may be due to increased hepatic production and this is consistent with the correlation with hepatic transaminases.

The physiological role of IGFBP-1 phosphorylation in regulating IGFBP-1 activity has not yet been elucidated. In vitro studies in which serine phosphorylation sites are mutated result in lower affinity of IGFBP-1 for IGF-I. Despite limited knowledge about the role of IGFBP-1 phosphorylation, the distribution of the phosphoisoforms are useful markers of sites of production. Non-pregnant serum IGFBP-1 originates from liver and circulates as a single, highly phosphorylated species. In maternal serum, IGFBP-1 exists in this highly phosphorylated state and also partially in non-phosphorylated isoforms. The highly phosphorylated form is likely to be hepatically derived, and the other forms—present at lower concentrations—are likely to be of decidual origin. So as discussed in the present study, to further investigate the relationships between polymorphisms of *IGFBP-1* gene and the pathophysiology of PE, specifying the site of IGFBP-1 production by identifying the phosphoisoforms may be profitable.

SNP analysis is a pivotal tool for investigating the relationship between genes and diseases. In the present study, authors have investigated the association between *IGFBP-1* gene polymorphisms and the risk of PE. This helps in unraveling the pathophysiology underlying PE development and identifying genetic or molecular agents for early prediction, prevention, and treatment.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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