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Recent Insights into the Role of the Insulin-Like Growth Factor Axis in Preeclampsia

Dimitra Kappou¹, Nikos Vrachnis² and Stavros Sifakis¹

¹*Department of Obstetrics-Gynecology, University Hospital of Heraklion, Crete,*

²*2nd Department of Obstetrics & Gynecology, Aretaieion Hospital, University of Athens, Athens, Greece*

1. Introduction

Preeclampsia, a hypertensive disorder that complicates approximately 3-5% of first pregnancies and is usually clinically manifested after 20 weeks of gestation, is a major cause of perinatal morbidity and mortality; also, neonates of preeclamptic mothers are prone to preterm birth, low birth weight for gestational age and fetal growth restriction [Goldman-Wohl & Yagel, 2002]. Although the pathophysiologic process of preeclampsia is not fully elucidated, abnormal placentation, shallow endovascular invasion, placental hypoxia, maternal insulin resistance and diffuse endothelial dysfunction seem to be interconnected key events that may precede the clinical onset of the disease by weeks or months [Davison et al., 2004]. In particular, impaired placental perfusion is evident even from the first trimester as it has been documented by the findings of both histologic and Doppler ultrasound findings of the uterine arteries and the altered levels of placental derived biochemical markers as pregnancy-associated plasma protein (PAPP-A) [Poon et al., 2009a; Poon et al., 2009b].

The insulin-like growth factor (IGF) system comprises the IGF peptides (IGF-I, IGF-II), the cellular IGF receptors (type I, type II), and a family of soluble high affinity IGF binding proteins (IGFBP-1 to IGFBP-6) which modulate the bioavailability and activity of the IGFs [Jones & Clemmons, 1994] (Figure 1). Since the discovery of the IGF system before 50 or so years, there is ample evidence for their role in cell proliferation, differentiation and migration and their anti-apoptotic properties as well; thus they are involved in several physiological and pathological processes during prenatal and postnatal life [Forbes & Westwood, 2008]. This review aims to critically evaluate the postulated role of IGF axis components in the pathogenesis of preeclampsia and to discuss the mechanisms through which these effects are mediated.

1.1 The IGF system in pregnancy

During pregnancy, several alterations are noted regarding the expression pattern and function of IGFs. According to a recent longitudinal study, the maternal serum levels of IGF-I remain stable until 20 weeks and then increase whereas IGF-II values do not relatively change throughout gestation [Olausson et al., 2008]. Though in non-pregnant-individuals,

IGF-I is primarily derived from the liver, during gestation its main source is decidua under the stimulatory action of a specific growth hormone placental variant (PGH) that is produced by syncytiotrophoblast and extravillous trophoblast from the 7th or 8th week of gestation and gradually replaces pituitary growth hormone (GH) in the maternal circulation. PGH is implicated in the physiological adjustment to gestation by stimulating gluconeogenesis, lipolysis and anabolism and exercises its effects either indirectly by regulating IGF-I levels or in an autocrine/paracrine manner [Sifakis et al., 2009]. In plasma during postnatal life, most of the IGFs (75%) exist in a 140-k Da heterotrimeric complex consisting of IGFBP-3 and an -85 kDa protein, the acid-labile (ALS); when this complex dissociates, IGFs form smaller, binary complexes with the other IGFBPs while less than 1% of IGFs circulate in free biologically active form [Baxter, 1994].

Fig. 1. A simplified model of the components of the IGF axis and their role in placental development

Despite many similarities, IGFBPs have distinctive properties concerning their exact function, their constant hormonal and metabolic regulation, their structural features and the tissue distribution of their expression during the various stages of development. Although in the non-pregnant state, IGFBP-I is mainly produced in the liver, during pregnancy its predominant site of synthesis is the decidualized endometrium [Forbes & Westwood, 2008]. In particular, IGFBP-1 is increasing rapidly in maternal serum so as to be abundant in second- and third-trimester concomitantly with the second wave of trophoblast invasion until 35 weeks and then decrease thereafter till term [Olausson et al., 2008]. IGFBP-3, the most abundant binding protein for IGFs, provides a circulating storage reservoir for IGFs although its affinity may be decreased in gestation period. An endogenous pregnancy-related serum IGFBP-3 proteolytic activity is considered a fundamental mechanism to increase bioactive IGFs [Lewitt et al., 1998]. Conflicting results have been reported regarding IGFBP-3 concentration throughout pregnancy probably as a result of different applied measurement methods; a recent longitudinal study reported that the maternal serum levels of IGFBP-3 remained stable and increased only after 35 weeks of gestation [Olausson et al., 2008]. The exact impact of IGFBPs also depends on the posttranslational modification of the protein (e.g. phosphorylation, glycosylation, altered proteolysis) which is under rapid and dynamic regulation [Forbes & Westwood, 2008]. Specifically, the IGFBP-I gene has multiple regulatory elements in its promoter that synergize or act independently and it is strongly regulated by insulin though IGFBP-3 is primarily determined by GH [Powell et al., 1995]. Besides, IGFBPs, particularly IGFBP-1, -3 and -5, carry out IGF-independent actions including inhibition of cell growth and induction of apoptosis; however their downstream effects need further investigation [Cohen et al., 1993; Jones et al., 1993].

The biological actions of both IGFs are mediated by binding to the two IGF receptors [Monzavi & Cohen, 2002]. The type I IGF receptor (IGF1R), a member of the protein tyrosine kinase receptor superfamily, is the main receptor for signal transduction and cellular action of the IGFs though the type II IGF receptor is identical to the mannose-6-phosphate receptor which shuttles lysosomal enzymes and binds IGF-II and (to a lesser extent) IGF-I [Monzavi & Cohen, 2002]. Another type of receptor which is also expressed in the placenta and binds to IGF-II in fetal tissues with similar affinity to IGF1R is the insulin receptor (IR) that is structurally similar to IGF1R but with a distinct signaling pathway mainly mitogenic [Frasca et al., 1999].

2. IGF system in fetal growth and preeclampsia

2.1 The role of the IGF system in fetal growth

An increasing wealth of literature including clinical and knockout studies in mice points to the crucial role of IGF axis in correct embryonic and placental development and growth. Regarding the role of IGF-I in fetoplacental growth, clinical studies based on the measurements in cord blood from healthy newborns demonstrated that birth weight is positively correlated with IGF levels and therefore, the levels are low and raised in small-for gestational-age (SGA) infants and large-for gestation-age (LGA) infants retrospectively [Giudice et al., 1995; Osorio et al., 1996; Boyne et al., 2003]. These clinical observations were further confirmed by studies using transgenic mice in which the mutation of the gene encoding either IGF-I or IGF-II resulted in restricted growth [Efstratiadis, 1998]. However, other research groups do not lend support to a relationship between total IGF-I and birth

weight [Chellakooty et al., 2003]. Surprisingly, increased transcription of IGF-I and IGF-II not essentially associated with a corresponding increase in proteins levels have also been noted in IUGR pregnancies interpreted as a compensatory attempt against the inhibitory effect of either the enhanced level of IGFBPs and/or number of IGF2R or a response to impaired growth [Dalcik et al., 2001; Sheikh et al., 2001]. Alternatively, maternal diabetes seems to result in inverse changes of circulating fetal IGF-I and IGFBP-1 at birth leading to the proposal that a decrease in IGFBP-1 and to a lesser extent an increase in IGFs of cord blood samples may represent an important mechanism that contributes to macrosomia in these pregnancies [Lindsay et al., 2007].

Additionally, extensive data are available on the involvement of the IGFBPs in the abnormal fetal growth and maturity, chiefly highlighting the role of IGFBP-1 & IGFBP-3 in this process. Several research groups support that IGFBP-1 concentrations in amniotic fluid, maternal serum and fetal cord blood are predictive of newborn birth weight in both humans and mice; particularly, a striking inverse correlation between IGFBP-1 levels and fetal size is established although it is not clarified if an elevated level of circulating IGFBP-I is sufficient to cause fetal growth retardation or it depends on IGF-I mediated cell proliferation [Chard 1994; Crossey et al., 2002]. In contrast to IGFBP-1 and IGFBP-2 which correlate inversely with IGF-1 levels and birthweight, IGF-I and IGFBP-3 appear to be regulated in a coordinated manner, and show a significant positive relationship to parameters of fetal growth in both normal and complicated pregnancies despite the narrow reported conflicting results [Fant et al., 1993; Verhaeghe et al., 1993]. However, there are also reports of elevated IGFBP-3 levels in SGA infants and in low-birth weight offspring of mice over expressing the human IGFBP-3 gene [Holmes et al., 1997; Modric et al., 2001]. Also, disrupted IGF receptors' expression can also negatively affect fetal growth as it is demonstrated by a recent study reporting severe fetal growth restriction in two infants with a heterozygous missense mutation in the IGFIR gene [Walenkamp et al., 2006]. On the contrary, IGF-2R is thought to clear the IGF-II from the circulation and this is obviously supported by studies showing that mice lacking the IGF2R have greater birth weights than wild-type littermates [Lau et al., 1994; Efstratiadis, 1998].

2.2 The role of IGF system in preeclampsia

A central feature of preeclampsia is defective placentation expressed as shallow placental invasion limited to the superficial portion of decidua and abnormal remodeling of the endometrial vasculature due to failure of the conversion of the maternal spiral arteries into vessels of low resistance and high capacitance, as it has been supported by histological analysis of preeclamptic tissue specimens [Goldman-Wohl & Yagel, 2002]. Indirect evidence for impaired placental perfusion in pregnancies destined to develop preeclampsia has been provided by Doppler studies of the uterine arteries which showed increased pulsatility index (PI) from the first trimester of pregnancy [Martin et al., 2001; Poon et al., 2009b]. Immunohistochemical studies in human and animal placentas have meticulously demonstrated the placental synthesis of IGF system components; however, it is not accurate to draw conclusions for the development of human placenta based on animal models as the placenta is one of the very few organs that is unique to each species, both anatomically and functionally.

The evolutionary pattern of expression of IGFs, IGFBPs and IGF-1R genes in the developing human placenta and fetal membranes has been described from as early as 6 weeks' gestation to term in order to detect the exact expression site of each peptide and the potential site of its action [Han et al., 1996]. Functionally, IGF axis appears to be involved in many aspects of placental development and metabolism both in uncomplicated and preeclamptic pregnancies though the exact signaling pathways have yet to be determined [Hills et al., 2004]. Studies based on cultured human trophoblast cells and cell lines propose that IGFs promote proliferation, regulate trophoblast migration and the differentiation of cytotrophoblasts into syncytiotrophoblasts and extravillous cells, enhance the proliferation and survival of placental fibroblast, exhibit anti-apoptotic effect and mediate nutrient availability at the fetoplacental unit [Lacey et al., 2002; Smith et al., 2002; Miller et al., 2005].

To date, the majority of published studies carried out to describe the alteration profile of the components of the IGF axis in preeclampsia are based on assays in maternal serum specimens. The extracted results do not always reflect the placental expression of the studied factors as the liver is an additional source of circulating factors in maternal serum or other posttranscriptional and/or posttranslational modifications maybe involved as it has been proposed for FGR placentas [Shin et al., 2003]. Regarding the early stages of gestation, when preeclampsia is in a pre-symptomatic stage, the published results are mainly focused on IGFs, IGFBP-1 and IGFBP-3 and are limited compared to the later stages where there is also discrepancy but to a lesser extent. The comparative analysis of these studies is a challenging task for several reasons such as the conflicting results, the differences in the study design, the sampling weeks, the dissimilar distribution of the severity and the subtypes of preeclampsia analyzed, the selection of the study population, the portion of each factor measured (total, bounded or free form) and the limitations of each study. Differentiations in the sensitivity and specificity of assays applied and the adjustment for confounding factors may also account for some of the variations observed across studies.

2.3 IGFs

Several studies have accessed the interesting way in which the trophoblast-derived IGF-II and the decidual-derived IGFBP-I interact in the uterine environment in a paracrine manner and how this modulates trophoblast invasion in preeclampsia [Giudice et al., 1999; Irwin et al., 2001; Shin et al., 2003]. IGF-II mRNA is highly expressed by trophoblast with the greatest concentrations expressed at the invading front even from the 6th week of gestation, indicating a possible role of this peptide in cytotrophoblastic proliferation and the decidualization of the maternal stroma while IGFBP-I is the most plentifully expressed binding protein in the decidualized endometrium under the stimulatory effect of HCG and progesterone [Moy et al., 1996; Fowler et al., 2000]. Interestingly, the mean IGFBP-I mRNA and protein level were significantly elevated in preeclampsia compared with uncomplicated pregnancies in positive correlation with the severity of the disease [Shin et al., 2003]. In line with this observation, Giudice et al indicated the possible involvement of this protein in abnormal placentation and the same research group supported that the decidual derived IGFBP-I may lead to high maternal serum concentrations due to the increased vascular permeability of the leaky capillaries common in preeclampsia [Giudice et al., 1997]. As for the IGF-II, a significant decrease more profound in severe preeclampsia was confirmed both

in m RNA and protein expression in preeclamptic placentas, by different research groups [Giudice et al., 1999; Shin et al., 2003]. Published data indicate that IGF-II stimulates proliferation and migration of cytotrophoblasts, regulates nutrient exchange but is not implicated in placental cell differentiation so the decreased levels of this factor may alter the invasive nature of cytotrophoblasts resulting in placental dysfunction [Shin et al., 2003]. On the contrary, Gratton et al. observed increased IGF-II m RNA abundance in the intermediate trophoblast surrounding placental infarcts suggesting a role in placental repair or remodeling and decreased IGFBP-1 m RNA levels [Gratton et al., 2002]. Besides, in an *in vivo* analysis of term placentas of gestations complicated by acute or chronic hypoxic ischemia, IGF-2 m RNA levels were elevated only in chronic hypoxia in contrast to IGF-I and PGH m RNA levels which did not significantly change, maybe as a part of a local metabolic adjustment [Trollmann et al., 2007].

IGF-II level in maternal serum is less investigated and up to now it seems not to significantly vary between preeclamptic and normotensive women [Giudice et al., 1997; Lewitt et al., 1998]. A possible explanation is that it does not share exactly the same regulation pattern with IGF-I as it is not primarily GH-dependent [Giudice et al., 1997]. On the contrary, there is a remarkable inconsistency among published results about the concentration of IGF-I in pregnancies destined to be preeclamptic. The only prospective cohort study that measured free rather than total IGF-I and IGFBP-1 levels and made adjustment for several confounding factors such as gestational age at blood collection, maternal age, parity, and prepregnancy adiposity, reported lower concentrations of these factors apparent in first trimester [Ning et al., 2004]. The attenuation of IGF-1 synthesis may result from impaired PGH synthesis as a consequence of the compromised placentation observed in preeclampsia [Ning et al., 2004]. Although several cross-sectional and longitudinal studies have found a positive correlation between serum PGH and IGF-1 values in pregnancies with fetoplacental unit disorders, our recent results do not provide support to the upper speculation as lower IGF-I levels but no alteration in PGH levels were observed in 11-13 weeks of gestation in pregnancies subsequently complicated by preeclampsia of either early or late onset [Sifakis et al., 2010; Sifakis et al. 2011a]. To elucidate this matter, it would be of special interest to investigate the range of the IGF-I levels in parallel with the change of PGH production throughout the disease transition from a latent preclinical stage to the clinically manifested preeclampsia.

Given that IGF-I acts positively on insulin sensitivity and the tissue availability of IGF-I is a significant determinant of insulin sensitivity in patients with essential hypertension, it could be presumed that decreased circulating levels of this factor would be responsible, at least in part, for insulin resistance in preeclampsia [Kocyigit et al., 2004]. However, Bartha et al. supported that increased insulin resistance is associated with gestational hypertension rather than preeclampsia and that there is no significant correlation between insulin sensitivity index and serum IGF-I levels [Bartha et al., 2002]. Also, there is no obvious explanation for the findings of other studies which recruited women before the clinical manifestation of the disease and reported that the maternal serum levels of IGF-I were either increased or not significantly altered [Hubinette et al., 2003; Vatten et al., 2008]. Based on a similar prospective approach, an increase in IGF-I from the first to second trimester and not within each trimester was associated with higher risk of preterm preeclampsia possibly interpreted as a compensatory mechanism to preserve fetal growth or/and a possible

accelerated proteolysis of IGFBPs [Vatten et al., 2008]. Along with this thesis, a recent study demonstrated elevated second trimester levels of PGH in women, who later developed preeclampsia associated with intrauterine growth restriction leading to greater availability of nutrients for the fetoplacental unit [Papadopoulou et al., 2006]. However, we cannot offer an explanation for the apparent delay from first to second trimester for such a placental response.

Regarding the period that follows the clinical manifestation of preeclampsia, IGF-I levels seem to markedly decrease in preeclamptic subjects, particularly in the severe subtype of this disorder [Halhali et al., 2000; Ingec et al., 2004; Altinkaynak et al., 2003]. Even though it could be the result of the compromised production of placental PGH, relative studies based on a single point-in-time observations in preeclamptic pregnancies complicated further or not by fetal growth restriction are inconsistent and a longitudinal description of the correlation between IGF-I and PGH in different trimesters is lacking [Mittal et al., 2007; Schiessl et al., 2007]. In contrast, two different research groups reported no difference between IGF-I values in preeclamptic women and normotensive controls, the one referred to preeclamptic women with late-onset disease and the other recruited women with preeclampsia of all subtypes [Lewitt et al., 1998].

2.4 IGFBPs

2.4.1 IGFBP-1

A lot of controversy exists regarding the role and the precise mechanisms of action of IGFBP-I at the maternal-fetal interface. On the one hand, IGFBP-I may act as a maternal restraint to trophoblast invasion via its inhibitory effect on mitogenic IGFs in decidual microenvironment [Ritvos et al., 1998]. On the other hand, Gleeson et al. doubt these results showing that IGFBP-I potentiates directly the human trophoblast migration by binding of its RGD domain (Arg-Gly-Asp) to the $\alpha 5 \beta 1$ integrin/fibronectin receptor on invading trophoblast leading to activation of mitogen activated protein kinase (MAPK) pathway [Gleeson et al., 2001]. This hypothesis is consistent with the observation that the regulation of $\alpha 3$, $\alpha 5$, $\beta 1$, $\beta 4$ integrin subunits (classes of adhesion molecules receptors) in trophoblast cells is altered in preeclamptic pregnancies [Zhou et al., 1993]. In vivo, it is still questionable which pathway of IGFBP-1 action is deregulated resulting in net suppression on trophoblast invasion.

A possible source of this inconsistency is the altered post-translational modification of IGFBP-1 in pregnant women [Forbes & Westwood, 2008]. In the circulation of non-pregnant women, IGFBP-1 exists only in its phosphorylated state (p-IGFBP-1) with high affinity for IGFs whereas during pregnancy, IGFBP-1 is extensively dephosphorylated to non-phosphorylated and intermediately phosphorylated isoforms (np-IGFBP-I) with a 6-fold lesser binding affinity for IGF-I and similar affinity for IGF-II [Westwood et al., 1994]. The functional significance of this modification is highlighted by the finding that np-IGFBP-1 enhanced the metabolic actions of IGF-I in nutrient transport in contrast to the inhibitory phosphorylated isoform [Yu et al., 1998]. A more complete interpretation of the data requires consideration of the distribution of the phosphoisoforms of IGFBP-I accompanying preeclampsia in each trimester of pregnancy.

De Groot et al. were the first who evaluated the midtrimester plasma level of IGFBP-1 in pregnancies destined to develop mild/moderate preeclampsia and observed lower circulating levels possibly due to the defective placentation that could affect the vascular deportation of this protein and/or its reduced hepatic synthesis [De Groot et al., 1996]. A more recent study underlined the fact that in a subgroup of women with coexisted White A diabetes the concentration of the protein was especially low even before the clinical manifestation of the two diseases [Hietala et al., 2000]. This notification implies that hyperinsulinemia, an important factor in the pathogenesis of preeclampsia, may additionally affect the level of serum IGFBP-1 although their association is still enigmatic.

In non pregnant women, IGFBP-I is negatively regulated by insulin and prevents glucose uptake by muscle and hepatic cells, possibly through IGF-dependent pathways [Holly et al., 1998]. Therefore decreased IGFBP-I have been related to various states of hyperinsulinemia including women with hypertension and insulin resistance. The interconnection of these two distinct entities is underlined by a series of well established clinical observations as that pregnancy-induced hypertension is more common in women with impaired glucose tolerance, pregnant women with diabetes have a higher incidence of preeclampsia and hyperinsulinemia can be detected in women several years after their first preeclamptic pregnancy [Suhonen & Teramo, 1993]. Surprisingly, other investigators have reported normal insulin response to intravenous glucose tolerance tests in preeclamptic women or even that these women were more sensitive to insulin [Solomon et al., 1994]. It is theorized that the negative relationship between insulin and IGFBP-1, typical of non-pregnant state, persists throughout normal pregnancy but seems to be lost in the early stages of pregnancies destined to become preeclamptic and either insulin starts to have a stimulatory effect on IGFBP-1 or both are regulated by another factor associated to preeclampsia such as hypoxia [Anim-Nyame et al., 2003]. However, in a longitudinal study, the circulating IGFBP-1 concentrations were found to be lower in serial samples obtained from women destined to develop preeclampsia indicating that IGFBP-1 is unlikely to act via its IGF-mediated effect and may actually promote trophoblast function acting through a signaling IGF-independent pathway [Anim-Nyame et al., 2000]. Concurrently, relatively low concentrations of IGFBP-1 both in the first and second trimesters were related to higher risk of term and in a lesser extent for preterm preeclampsia as it is noted in non-pregnant women with a higher prevalence of metabolic syndrome [Vatten et al., 2008]. This differentiation may further reflect two distinct clinical entities, as preterm preeclampsia is a clinically more severe form often accompanied by fetal restricted growth due to the placental disease in contrast to term preeclampsia in which placental perfusion and fetal growth are often normal and the main pathophysiological processes resemble those of the metabolic syndrome with an increase in adipose tissue and impaired glucose and lipid metabolism.

In pregnancies with established disease, IGFBP-1 levels are grossly elevated in the majority of the research studies with older studies supporting a positive correlation with severity of the disease and recent studies the opposite [Giudice et al., 1997; Ingec et al., 2004]. This fluctuation in serum levels in relation to the clinical onset of preeclampsia has also been reported for other placental proteins, such as PAPP-A. Elevated circulating peptide levels may reflect the increased synthesis of IGFBP-1 from decidual cells which in turn may play a role in the shallow implantation, characteristic of preeclampsia. In another prospective study, IGFBP-I concentration was found augmented at the time of delivery only in preeclampsia complicated

further by IUGR demonstrating that this change may simply reflect low birthweight in these cases or alternatively the higher incidence of IUGR in severe preeclampsia [Wang et al., 1996].

2.4.2 Other IGFBPs

In addition to the decidua basalis and parietalis, IGFBP-3, IGFBP-4, and IGFBP-5 are expressed in fetal cells with IGFBP-3 being the most prominent [Han et al., 1996]. Interestingly, the cleavage of IGFBP-3 into fragments during pregnancy except from increasing the availability of IGFs may have additional significance as in the same time these fragments can exert IGF-independent biological activity [Firth & Baxter, 2002]. Concerning the role of IGFBP-3 in preeclampsia, a study designed to detect genes associated to increased apoptosis in preeclamptic placentas showed a strong down regulation pattern leading to lower IGF-mediated anti-apoptotic effect causing placental dysfunction [Han et al., 2006]. In future, the interaction of some IGFBPs with other placental-produced factors should be also investigated. PAPP-A, a useful early marker of preeclampsia, has been identified as protease to IGFBP-3 and -4 so its lower levels observed in preeclampsia might diminish the amount of IGFs being available for cell uptake and growth stimulation [Cowans et al., 2007].

IGFBP-3, the major carrier for IGFs in plasma during pregnancy is the only studied binding protein in maternal serum from preeclamptic pregnancies. The only so far published study that reported no change in IGFBP-3 levels in early stages of gestation is opposite to recent data that demonstrate an increase in IGFBP-3 concentration at 11-13 weeks in term but not in preterm preeclampsia not associated to uterine artery PI which is a known measure of impaired placental perfusion [Sifakis et al., 2011b]. Most likely, this finding could be the result of impaired glucose tolerance and increased insulin resistance as there is in vitro and in vivo evidence for a relationship between circulating IGFBP-3 levels and hyperglycemia and a IGFBP-3 potent insulin-antagonizing capability exerted either via IGF-independent pathways or by decreasing IGF-bioavailability. After the clinical establishment of preeclampsia, there is inconsistency among reported results as both a reduction and no change in its levels have been demonstrated [Altinkaynak et al., 2003; Wang et al., 1996].

3. Conclusion

Overall, it is still uncertain if the deregulation of the tuned balance among IGF system components possesses a crucial role in the pathogenesis of preeclampsia or is just a mere consequence of the disease. From this summary of relevant research, it is not yet plausible to determine the magnitude of possible associations, if any, between varying concentrations of IGFs and IGFBPs in maternal circulation and preeclampsia risk. Hopefully, the quantification of maternal plasma levels of the peptides of the IGF family may utilize as a predictive screening test to select pregnant women at increased risk for developing preeclampsia who may be favored from the administration of aspirin or other antiplatelet therapy or more intense sonographic surveillance, optimally as the only parameter or combined with other known independent indicators of preeclampsia risk. Clearly, much additional research is warranted including longitudinal studies with serial measurements of these factors and molecular clarification of the signaling pathways of each component intending to novel diagnostic interventions and to cast further light on the pathogenesis of preeclampsia as well.

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Obstetrics is evolving rapidly and finds itself today at the forefront of numerous developments. Providing selected updates on contemporary issues of basic research and clinical practice, as well as dealing with preconception, pregnancy, labor and postpartum, the present book guides the reader through the tough and complex decisions in the clinical management. Furthermore, it deepens the scientific understanding in the pathogenetic mechanisms implicated in pregnancy and motivates further research by providing evidence of the current knowledge and future perspectives in this field. Written by an international panel of distinguished authors who have produced stimulating articles, the multidisciplinary readers will find this book a valuable tool in the understanding of the maternal, placental and fetal interactions which are crucial for a successful pregnancy outcome.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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Phone: +86-21-62489820
Fax: +86-21-62489821

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