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Maternal serum insulin-like growth factor-binding protein-1 (IGFBP-1) at 11–13 weeks in pre-eclampsia

Stavros Sifakis[1], Ranjit Akolekar[2], Dimitra Kappou[1], Nikitas Mantas[2] and Kypros H. Nicolaides[2,3]*

[1]*Department of Obstetrics and Gynaecology, University Hospital of Heraklion, Crete, Greece*
[2]*Department of Fetal Medicine, King's College Hospital, London, UK*
[3]*Department of Fetal Medicine, University College Hospital, London, UK*

Objective The aim of this study was to determine the maternal serum concentration of insulin-like growth factor-binding protein-1 (IGFBP-1) at 11–13 weeks' gestation in pregnancies that subsequently develop pre-eclampsia (PE) and to examine the possible association with uterine artery pulsatility index (PI).

Methods Maternal serum concentration of IGFBP-1 and uterine artery PI were measured in 60 cases that developed PE, including 20 that required delivery before 34 weeks (early-PE) and 120 unaffected controls. The measured IGFBP-1 concentration and uterine artery PI were converted into a multiple of the expected median (MoM) in unaffected pregnancies and median MoM values were compared in the outcome groups. Regression analysis was used to determine the significance of association of IGFBP-1 MoM with uterine artery PI MoM.

Results In the early- and late-PE groups, the median IGFBP-1 was decreased (0.63 and 0.67 MoM, respectively) and uterine artery PI was increased (1.31 and 1.19 MoM, respectively). In the group that developed PE there were no significant associations between serum IGFBP-1 with uterine artery PI ($p = 0.210$).

Conclusion In pregnancies that develop PE, the serum IGFBP-1 is decreased from the first trimester suggesting that IGFBP-1 may be implicated in the pathogenesis of PE in a mechanism unrelated to impaired placental perfusion. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: first-trimester screening; insulin-like growth factor-binding protein-1; pre-eclampsia; pregnancy-associated plasma protein-A; uterine artery Doppler

INTRODUCTION

Pre-eclampsia (PE), which affects approximately 2% of pregnancies, is a major cause of maternal and perinatal morbidity and death (ACOG, 2002). There is an emerging evidence that PE is a heterogeneous condition with early disease requiring delivery before 34 weeks, thought to be a consequence of impaired placentation (Meekins *et al*., 1994; Yu *et al*., 2005; Plascencia *et al*., 2007), whereas in late-PE the main pathophysiological processes resemble those of the metabolic syndrome with increased insulin resistance (Kaaja *et al*., 1995; Lorentzen *et al*., 1998; Vatten and Skjaerven, 2005; D'Anna *et al*., 2006).

Several studies have demonstrated that in pregnancies complicated by PE, both during and before the clinical onset of the disease the circulating maternal concentrations of insulin-like growth factor-binding protein-1 (IGFBP-1) are altered (Table 1), suggesting that IGFBP-1 may be implicated in the pathogenesis of the disease. However, it is not clear whether the relation between IGFBP-1 and PE is the consequence of its actions on placentation or its effects on insulin resistance and the metabolic syndrome. During pregnancy IGFBP-1 is produced by decidualized endometrial cells (Han *et al*., 1996; Giudice and Irwin, 1999) and has a direct effect on the interaction between the decidua and the invading trophoblast (Han *et al*., 1996; Giudice and Irwin, 1999; Lee *et al*., 1997; Fowler *et al*., 2000). In addition, IGFBP-1 is involved in placentation and insulin resistance indirectly through its effects on IGF-I. This binding protein prolongs the half-life of IGF-I in plasma (Rechler and Clemmons, 1998; Monzavi and Cohen, 2002), and previous studies reported that IGF-I regulates and enhances trophoblast invasion by stimulation of cell migration and proliferation (Aplin *et al*., 2000; Fowler *et al*., 2000; Lacey *et al*., 2002; Forbes and Westwood, 2008). In addition, IGFBP-1 plays a role in maternal metabolism and the maintenance of glucose levels by preventing glucose uptake by muscle and hepatic cells through its inhibitory effects on IGF-I (Baxter, 1995; Lee *et al*., 1997).

The aims of our study were first, to investigate the maternal serum concentration of IGFBP-1 at 11–13 weeks in pregnancies that subsequently develop PE and second, to examine whether the possible relation of IGFBP-1 to PE is mediated by an effect on placentation manifested in increased uterine artery pulsatility index (PI), which provides a measure of placental perfusion

*Correspondence to: Kypros H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
E-mail: kypros@fetalmedicine.com

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Table 1—Studies reporting the maternal circulating IGFBP-1 levels (ng/mL) in patients during or before PE compared to unaffected controls

Author	Gestation (week)	Control		PE	
		n	IGFBP-1	*n*	IGFBP-1
During PE					
Giudice *et al*. (1997)	20–34	29	77	16	428*
Lewitt *et al*. (1998)	26–39	11	317	10	404
Anim-Nyame *et al*. (2000)	36	12	134	10	192*
Ingec *et al*. (2004)	28–40	20	249	60	350*
Before PE					
de Groot *et al*. (1996)	14–27	20	79	20	36*
Anim-Nyame *et al*. (2000)	16	12	134	10	64*
Hietala *et al*. (2000)	14–17	794	103	34	73*
Grobman and Kazer (2001)	14–28	24	130	12	84*
Ning *et al*. (2004)	8–16	477	53	53	39*

IGFBP-1, insulin-like growth factor-binding protein-1; PE, pre-eclampsia.
* Significance level $p < 0.05$.

and is known to be increased in pregnancies that subsequently develop PE (Plascencia *et al*., 2007; Akolekar *et al*., 2011).

MATERIALS AND METHODS

Study population

This was a case–control study drawn from a large observational prospective study for hypertensive complications of pregnancy in women attending for their routine first hospital visit during pregnancy at King's College Hospital, London, UK. In this visit, which is held between week 11 and 13 weeks and 6 days of gestation, all women have an ultrasound scan to first, confirm gestational age from the measurement of the fetal crown–rump length (CRL), second, diagnose any major fetal abnormalities and third, measure fetal nuchal translucency (NT) thickness as part of screening for chromosomal abnormalities. In addition, the maternal serum PAPP-A and free beta-human chorionic gonadotrophin are determined and the results are combined with the fetal NT to calculate the patient-specific risk for trisomy 21 (Snijders *et al*., 1998; Kagan *et al*., 2008).

We recorded maternal characteristics and medical history, stored serum at −80 °C for subsequent biochemical analysis and performed transabdominal pulsed Doppler for measurement of the left and right uterine artery PI and recorded the mean (Plascencia *et al*., 2007; Akolekar *et al*., 2011). Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

There was available stored maternal serum from 20 cases that developed PE requiring delivery before 34 weeks (early-PE) and 40 cases that developed late-PE. Each case of PE was matched with two controls who had blood collected on the same day and delivered a phenotypically normal neonate appropriate for gestational age at term and did not develop any hypertensive disorder of pregnancy. None of the samples in the case–control study was previously thawed and refrozen.

Maternal history

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and Mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or ovulation induction drugs), medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome and thrombophilia), medication (including anti-hypertensives, insulin and aspirin), parity (parous or nulliparous if no delivery beyond 23 weeks), obstetric history (including previous pregnancy with PE) and history of PE in the mother (yes or no). The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured, and the body mass index (BMI) was calculated in kg/m^2.

Outcome measures

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy (Brown *et al*., 2001). The systolic blood pressure should be 140 mm Hg or more and the diastolic blood pressure should be 90 mmHg or more on at least two occasions 4 h apart developing after 20 weeks of gestation together with significant proteinuria in previously normotensive women. Significant proteinuria is defined by 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the

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presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).

Sample analysis

Serum samples were used to measure IGFBP-1 concentration by a quantitative enzyme linked immunoassay technique using DSL-10-7800 IGFBP-1 assay (Diagnostic systems laboratories, Inc. Webster, TX, USA). The lower limit of detection of the assay for IGFBP-1 was 0.25 ng/mL.

Statistical analysis

The following steps were taken for the statistical analysis. The distribution of IGFBP-1 was normally distributed and did not require any transformation. The distribution of uterine artery PI was made Gaussian after logarithmic transformation. Multiple regression analysis was used to determine which of the factors among the maternal characteristics and gestation were significant predictors of IGFBP-1 in the unaffected group. Each value in the unaffected and PE group was then converted into multiple of the unaffected median (MoM) after adjustment for those characteristics found to be significant in the multiple regression analysis. Similarly, the measured uterine artery PI was converted into MoM after adjustment for gestation, maternal age and weight, smoking status and racial origin (Akolekar *et al*., 2011). Mann–Whitney *U*-test with *post hoc* Bonferroni correction was used to compare median MoM values IGFBP-1 and uterine artery PI between the outcome groups. Regression analysis was used to determine the significance of association between maternal serum IGFBP-1 and uterine artery PI in the outcome groups. The *a priori* risks for early- and late-PE based on maternal characteristics were determined as previously described and were then logarithmically transformed (Akolekar *et al*., 2011). Logistic regression analysis was used to determine if the log-transformed *a priori* risks, log uterine artery PI MoM and IGFBP-1 MoM had a significant contribution in predicting early- and late-PE. The detection and false-positive rates were calculated as the respective proportions of PE (detection rate) and unaffected pregnancies (false-positive rate) with MoM values above given cut-offs. The performance of screening was determined by receiver operating characteristic curves analysis.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

RESULTS

The maternal characteristics of the outcome groups are compared in Table 2. In the group that developed early-PE compared to the unaffected group, women were younger, there were more African women, more women had PE in their previous pregnancy and their mother had PE, and more women had chronic hypertension and were receiving anti-hypertensive medication. In the group that developed late-PE, compared to the unaffected group, women had a significantly higher BMI, there were more African women, more women had PE in their previous pregnancy and had chronic hypertension.

Unaffected group

Multiple regression analysis in the unaffected group demonstrated that IGFBP-1 significant independent contributions were provided by African racial origin but not by fetal CRL ($p = 0.514$), maternal weight ($p = 0.06$), smoking status ($p = 0.658$), parity ($p = 0.110$) or method of conception ($p = 0.07$):

$$\text{Expected IGFBP-1} = 80.42 + (-31.17 \text{ if African racial origin, } 0 \text{ if any other});$$
$$r^2 = 0.106,\ p < 0.0001.$$

In the unaffected group, there was no significant association between IGFBP-1 MoM and uterine artery PI MoM ($r = 0.177$; $p = 0.053$).

PE group

In the pregnancies that subsequently developed early- and late-PE, the median IGFBP-1 MoM was decreased and uterine artery PI was increased (Table 3).

In the group that developed PE there were no significant associations between serum IGFBP-1 with uterine artery PI ($p = 0.210$). There was a significant association between gestation at delivery and uterine artery PI MoM ($r = -0.378$; $p = 0.003$) but not IGFBP-1 MoM ($p = 0.614$).

The patient-specific risk for early- and late-PE is calculated from the formula: odds/(1 + odds), where odds $= eY$ and Y is derived from multivariate logistic regression analysis of the disease-specific *a priori* risk, uterine artery PI MoM and IGFBP-1 MoM. Logistic regression analysis demonstrated that in the prediction of early-PE, there were significant contributions from log-transformed *a priori* risk [odds ratio (OR) 12.6, 95% confidence interval (CI) 3.4–46.1), log uterine artery PI MoM (OR 9.1E3, 95% CI 43.8–18.8E6; $p = 0.001$) and IGFBP-1 MoM (OR 0.18, 95% CI 0.04–0.89; $p = 0.035$). The estimated detection rate, at the false-positive rate of 5%, of screening for early-PE by a combination of the *a priori risk* and uterine artery PI MoM was 55% and this increased to 60% by addition of IGFBP-1 MoM. In the prediction of late-PE, addition of IGFBP-1 MoM did not provide a significant contribution in the performance of screening that was achieved by a combination of the *a priori* risk and uterine artery PI MoM ($p = 0.175$).

DISCUSSION

The findings of this study demonstrate that in pregnancies that develop PE, the maternal serum concentration of IGFBP-1 at 11–13 weeks is decreased and this

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Table 2—Maternal and pregnancy characteristics in the outcome groups

Maternal and pregnancy characteristics	Unaffected ($n = 120$)	Early-PE ($n = 20$)	Late-PE ($n = 40$)
Maternal age in years, median (IQR)	35.7 (31.8–39.5)	29.1 (23.7–34.0)*	32.5 (29.3–38.0)
Body mass index in kg/m^2, median (IQR)	23.8 (21.5–25.7)	26.3 (21.6–34.4)	27.3 (23.0–30.9)*
Gestation at sampling in days, median (IQR)	90 (86–93)	89 (85–91)	87 (85–90)*
Gestation at delivery in weeks, median (IQR)	40.0 (39.0–40.8)	31.4 (29.1–33.4)*	38.1 (36.6–39.6)*
Birth weight in kg, median (IQR)	3.5 (3.2–3.7)	1.4 (1.1–1.7)*	2.9 (2.5–3.2)*
Racial origin			
White, *n* (%)	96 (80.0)	8 (40.0)	21 (52.5)
African, *n* (%)	13 (10.8)	10 (50.0)*	17 (42.5)*
South Asian, *n* (%)	5 (4.2)	1 (5.0)	2 (5.0)
East Asian, *n* (%)	4 (3.3)	0	0
Mixed, *n* (%)	2 (1.7)	1 (5.0)	0
Parity			
Nulliparous, *n* (%)	48 (40.0)	9 (45.0)	15 (37.5)
Parous—no previous PE, *n* (%)	67 (55.8)	6 (30.0)	21 (52.5)
Parous—previous PE, *n* (%)	5 (4.2)	5 (25.0)*	4 (10.0)
History of PE in the mother *n* (%)	5 (4.2)	4 (20.0)*	2 (5.0)
Cigarette smoker, *n* (%)	8 (6.7)	1 (5.0)	5 (12.5)
Conception			
Spontaneous, *n* (%)	99 (82.5)	19 (95.0)	38 (95.0)
Assisted, *n* (%)	21 (17.5)	1 (5.0)	2 (5.0)
Medical history			
None, *n* (%)	112 (93.3)	14 (70.0)	32 (80.0)
Chronic hypertension, *n* (%)	0	3 (15.0)*	4 (10.0)*
Diabetes mellitus, *n* (%)	0	1 (5.0)	0
Thrombophilia, *n* (%)	3 (2.5)	0	0
Others, *n* (%)	5 (4.2)	2 (10.0)	4 (10.0)
Medication during pregnancy			
None, *n* (%)	114 (95.0)	14 (70.0)	35 (87.5)
Anti-hypertensives, *n* (%)	0	3 (15.0)*	1 (2.5)
Insulin, *n* (%)	0	1 (5.0)	0
Aspirin/heparin, *n* (%)	3 (2.5)	0	0
Others, *n* (%)	3 (2.5)	2 (10.0)	4 (10.0)

PE, pre-eclampsia; IQR, interquartile range.
Comparisons between outcome groups (chi-square test and Fisher exact test for categorical variables and Mann–Whitney *U*-test with *post hoc* Bonferroni correction for continuous variables).
* Significance level $p < 0.025$.

Table 3—Median (IQR) for maternal serum IGFBP-1 and uterine artery PI in the outcome groups

	Unaffected ($n = 120$)	Early-PE ($n = 20$)	Late-PE ($n = 40$)
IGFBP-1, median (IQR)			
MoM	1.01 (0.72–1.27)	0.63 (0.37–0.92)*	0.67 (0.43–0.98)*
ng/mL	78.6 (54.9–99.4)	40.9 (23.9–61.4)	48.8 (24.8–67.7)
Uterine artery PI, median (IQR)			
MoM	0.98 (0.79–1.23)	1.31 (1.07–1.65)*	1.19 (0.92–1.37)*
Unit	1.55 (1.23–1.95)	2.22 (1.66–2.64)	1.75 (1.44–2.31)

IQR, interquartile range; IGFBP, insulin-like growth factor-binding protein-1; PI, pulsatility index; PE, pre-eclampsia.
Comparisons between outcome groups by Mann–Whitney *U*-test with *post hoc* Bonferroni correction.
* Significance level $p < 0.025$.

decrease is similar in early- and late-PE. The decrease in IGFBP-1 is unrelated to impaired placental perfusion evident by increased PI in the uterine arteries which is particularly marked in early-PE.

In the unaffected controls, the measured concentration of maternal serum IGFBP-1 was lower in women of African racial origin but did not change significantly with other maternal or fetal characteristics. Consequently, as in the case of uterine artery PI the measured concentration of IGFBP-1 must be adjusted for the factors that affect its concentration in the unaffected population before comparing with pathological pregnancies (Akolekar *et al*., 2011). None of the previous studies have adjusted the measured concentration of IGFBP-1 for any potential maternal or fetal characteristics except Ning *et al*. (2004) who adjusted the IGFBP-1 levels for maternal age, ethnic origin, parity and family history of hypertension. A longitudinal study of 23 unaffected pregnancies at 8–35 weeks of gestation reported that the maternal serum levels of IGFBP-1 increased

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with gestational age until 35 weeks and then decreased thereafter till term (Olausson *et al.*, 2008). In our study, there was no significant change with fetal CRL within the narrow gestational range of 11–13 weeks.

Evidence suggesting a possible role for IGFBP-1 in the pathogenesis of PE is derived from reports that the concentration of this peptide in the maternal circulation is altered in women with PE (Table 1) and *in vitro* studies demonstrating decreased IGFBP-1 mRNA expression in placentae from pregnancies with PE (Gratton *et al.*, 2002). In pregnancies destined to develop PE, the circulating maternal levels of IGFBP-1 are decreased but in those with established disease the levels are increased (Table 1). This change in circulating levels from low to high in relation to the clinical onset of PE has also been reported for other placental proteins, such as pregnancy-associated plasma protein-A (Spencer *et al.*, 2006; Poon *et al.*, 2009).

The exact role of IGFBP-1 in placentation is controversial with some studies reporting that this protein inhibits trophoblastic invasion (Irwin and Giudice, 1998; Irwin *et al.*, 2001) and others suggesting that the opposite is true (Jones *et al.*, 1993; Gleeson *et al.*, 2001). There is extensive evidence that the underlying mechanism for early-PE is impaired trophoblastic invasion of the maternal spiral arteries and consequent decrease in placental perfusion (Meekins *et al.*, 1994; Yu *et al.*, 2005; Plascencia *et al.*, 2007). This is supported by our findings that in early-PE uterine artery PI is increased. However, our finding that in the PE group there was no significant association between serum IGFBP-1 and uterine artery PI does not lend support to the hypothesis that the involvement of IGFBP-1 in the pathogenesis of PE is mediated through the effect on placental perfusion.

In women destined to develop late-PE, 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, impaired glucose tolerance and increased insulin resistance (Kaaja *et al.*, 1995; Lorentzen *et al.*, 1998; Vatten and Skjaerven, 2005; D'Anna *et al.*, 2006). In non-pregnant women, insulin is the main regulator of IGFBP-1, and studies in pregnancy reported that IGFBP-I production by the decidualized stroma is inhibited by insulin (Thraikill *et al.*, 1990; Jones and Clemmons, 1995; Fowler *et al.*, 2000). It is possible that the low levels of IGFBP-1 in women destined to develop PE may be the consequence of the associated hyperinsulinemia and increased insulin resistance (Hietala *et al.*, 2000; Ingec *et al.*, 2004). We have previously reported that in both early- and late-PE, the maternal serum concentration of IGF-I at 11–13 weeks' gestation is decreased and this is unrelated to the increase in uterine artery PI (Sifakis *et al.*, 2010). Consequently, the effect of IGF-I and IGFBP-1 on PE is more likely to be related to their metabolic effects rather than their actions on placentation.

Original publication

All authors have read and approved the submission of this article; the article has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

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REFERENCES

ACOG Practice Bulletin. 2002. Diagnosis and management of preeclampsia and eclampsia. Number 33, 2002. ACOG Committee on Practice Bulletins—Obstetrics. *Obstet Gynecol* **99**: 159–167.

Akolekar R, Syngelaki A, Sarquis R, Wright D, Nicolaides KH. 2011. Prediction of preeclampsia from biophysical and biochemical markers at 11–13 weeks. *Prenat Diagn* **31**(1): 66–74.

Anim-Nyame N, Hills FA, Sooranna SR, Steer PJ, Johnson MR. 2000. A longitudinal study of maternal plasma insulin-like growth factor binding protein-1 concentrations during normal pregnancy and pregnancies complicated by pre-eclampsia. *Hum Reprod* **15**: 2215–2219.

Aplin JD, Lacey H, Haigh T, Jones CJ, Chen CP, Westwood M. 2000. Growth factor-extracellular matrix synergy in the control of trophoblast invasion. *Biochem Soc Trans* **28**: 199–202.

Baxter RC. 1995. Insulin-like growth factor binding proteins as glucoregulators. *Metabolism* **44**: 12–17.

Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. 2001. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* **20**: IX–XIV.

D'Anna R, Baviera G, Corrado F, *et al.* 2006. Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. *BJOG* **113**: 1264–1269.

de Groot CJ, O'Brien TJ, Taylor RN. 1996. Biochemical evidence of impaired trophoblastic invasion of decidual stroma in women destined to have preeclampsia. *Am J Obstet Gynecol* **175**: 24–29.

Forbes K, Westwood M. 2008. The IGF axis and placental function. *Horm Res* **69**: 129–137.

Fowler DJ, Nicolaides KH, Miell JP. 2000. Insulin-like growth factor binding protein-1 (IGFBP-1): a multifunctional role in the human female reproductive tract. *Hum Reprod Update* **6**: 495–504.

Giudice LC, Irwin JC. 1999. Roles of the insulin-like growth factor family in nonpregnant human endometrium and at the decidual: trophoblast interface. *Semin Reprod Endocrinol* **17**: 13–21.

Giudice LC, Martina NA, Crystal RA, Tazuke S, Druzin M. 1997. Insulin-like growth factor binding protein-1 at the maternal-fetal interface and insulin-like growth factor-I, insulin-like growth factor-II, and insulin-like growth factor binding protein-1 in the circulation of women with severe preeclampsia. *Am J Obstet Gynecol* **176**: 751–757.

Gleeson LM, Chakraborty C, McKinnon T, Lala PK. 2001. Insulin-like growth factor-binding protein 1 stimulates human trophoblast migration by signaling through alpha 5 beta 1 integrin via mitogen-activated protein kinase pathway. *J Clin Endocrinol Metab* **86**: 2484–2493.

Gratton RJ, Asano H, Han VK. 2002. The regional expression of insulin-like growth factor II (IGF-II) and insulin-like growth factor binding protein-1 (IGFBP-1) in the placentae of women with pre-eclampsia. *Placenta* **23**: 303–310.

Grobman WA, Kazer RR. 2001. Serum insulin, insulin-like growth factor-I, and insulin-like growth factor binding protein-1 in women who develop preeclampsia. *Obstet Gynecol* **97**: 521–526.

Han VK, Bassett N, Walton J, Challis JR. 1996. The expression of insulin-like growth factor (IGF) and IGF binding protein (IGFBP) genes in the human placenta and membranes: evidence for IGF-IGFBP interactions at the feto–maternal interface. *J Clin Endocrinol Metab* **81**: 2680–2693.

Hietala R, Pohja-Nylander P, Rutanen EM, Laatikainen T. 2000. Serum insulin-like growth factor binding protein-1 at 16 weeks and subsequent preeclampsia. *Obstet Gynecol* **95**: 185–189.

Ingec M, Gursoy HG, Yildiz L, Kumtepe Y, Kadanali S. 2004. Serum levels of insulin, IGF-I, and IGFBP-1 in pre-eclampsia and eclampsia. *Int J Gynaecol Obstet* **84**: 214–219.

Irwin JC, Giudice LC. 1998. Insulin-like growth factor binding protein-1 binds to placental cytotrophoblast alpha5beta1 integrin and inhibits cytotrophoblast invasion into decidualized endometrial stromal cultures. *Growth Horm IGF Res* **8**: 21–31.

Irwin JC, Suen LF, Faessen GH, Popovici RM, Giudice LC. 2001. Insulin-like growth factor (IGF)-II inhibition of endometrial stromal cell tissue inhibitor of metalloproteinase-3 and IGF-binding protein-1 suggests paracrine interactions at the decidua: trophoblast interface during human implantation. *J Clin Endocrinol Metab* **86**: 2060–2064.

Jones JI, Clemmons DR. 1995. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* **16**: 3–34.

Jones JI, Gockerman A, Busby WH Jr, Wright G, Clemmons DR. 1993. Insulin-like growth factor binding protein 1 stimulates cell migration and binds to the alpha 5 beta 1 integrin by means of its Arg-Gly-Asp sequence. *Proc Natl Acad Sci U S A* **90**: 10553–10557.

Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O. 1995. Serum lipoproteins, insulin, and urinary prostanoid metabolites in normal and hypertensive pregnant women. *Obstet Gynecol* **85**: 353–356.

Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. 2008. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin, and pregnancy associated plasma protein-A. *Ultrasound Obstet Gynecol* **31**: 618–624.

Lacey H, Haigh T, Westwood M, Aplin JD. 2002. Mesenchymally-derived insulin-like growth factor 1 provides a paracrine stimulus for trophoblast migration. *BMC Dev Biol* **2**: 5.

Lee PD, Giudice LC, Conover CA, Powell DR. 1997. Insulin-like growth factor binding protein-1: recent findings and new directions. *Proc Soc Exp Biol Med* **216**: 319–357.

Lewitt MS, Scott FP, Clarke NM, Wu T, Sinosich MJ, Baxter RC. 1998. Regulation of insulin-like growth factor-binding protein-3 ternary complex formation in pregnancy. *J Endocrinol* **159**: 265–274.

Lorentzen B, Birkeland KI, Endresen MJ, Henriksen T. 1998. Glucose intolerance in women with pre-eclampsia. *Acta Obstet Gynecol* **77**: 22–27.

Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, van Asshe A. 1994. A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. *BJOG* **101**: 669–674.

Monzavi R, Cohen P. 2002. IGFs and IGFBPs: role in health and disease. *Best Pract Res Clin Endocrinol Metab* **16**: 433–447.

Ning Y, Williams MA, Vadachkoria S, Muy-Rivera M, Frederick IO, Luthy DA. 2004. Maternal plasma concentrations of insulin-like growth factor-1 and insulin-like growth factor-binding protein-1 in early pregnancy and subsequent risk of preeclampsia. *Clin Biochem* **37**: 968–973.

Olausson H, Lof M, Brismar K, Lewitt M, Forsum E, Sohlstrom A. 2008. Longitudinal study of the maternal insulin-like growth factor system before, during and after pregnancy in relation to fetal and infant weight. *Horm Res* **69**: 99–106.

Plascencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. 2007. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* **30**: 742–749.

Poon LC, Maiz N, Valencia C, Plasencia W, Nicolaides KH. 2009. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. *Ultrasound Obstet Gynecol* **33**: 23–33.

Rechler MM, Clemmons DR. 1998. Regulatory actions of insulin-like growth factor-binding proteins. *Trends Endocrinol Metab* **9**: 176–183.

Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH, Fetal Medicine Foundation First Trimester Screening Group. 1998. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. *Lancet* **352**: 343–346.

Sifakis S, Akolekar R, Kappou D, Mantas N, Nicolaides KH. 2010. Maternal serum insulin-like growth factor-I at 11–13 weeks in preeclampsia. *Prenat Diagn* **30**: 1026–1031.

Spencer K, Yu CK, Savvidou M, Papageorghiou AT, Nicolaides KH. 2006. Prediction of pre-eclampsia by uterine artery Doppler ultrasonography and maternal serum pregnancy-associated plasma protein-A, free beta-human chorionic gonadotropin, activin A and inhibin A at 22 + 0 to 24 + 6 weeks' gestation. *Ultrasound Obstet Gynecol* **27**: 658–663.

Thraikill KM, Clemmons DR, Busby WH Jr, Handwerger S. 1990. Differential regulation of insulin-like growth factor binding protein secretion from human decidual cells by IGF-I, insulin, and relaxin. *J Clin Invest* **86**: 878–883.

Vatten LJ, Skjaerven R. 2004. Is pre-eclampsia more than one disease? *BJOG* **111**: 298–302.

Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH. 2005. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* **193**: 429–436.