

Maternal serum insulin-like growth factor-I at 11–13 weeks in preeclampsia

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Objective To investigate the maternal serum concentration of insulin-like growth factor-I (IGF-I) in the first trimester of pregnancies that subsequently develop preeclampsia (PE) and to examine the possible association with uterine artery pulsatility index (PI).

Methods The maternal serum concentration of IGF-I and uterine artery PI at 11–13 weeks were measured in 53 cases that developed PE, including 18 that required delivery before 34 weeks (early-PE) and 106 unaffected controls. The measured IGF-I 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. The significance of association of IGF-I MoM with uterine artery PI MoM was determined by regression analysis.

Results In the early-PE and late-PE groups, compared to the unaffected controls, the median IGF-I decreased (0.53 and 0.55 MoM, respectively) and uterine artery PI increased (1.55 and 1.21 MoM, respectively). In the group that developed PE, there was no significant association between serum IGF-I and uterine artery PI ($p = 0.632$).

Conclusion In pregnancies destined to develop PE, the circulating levels of IGF-I decrease from the first trimester of pregnancy suggesting that IGF-I may be implicated in the pathogenesis of the disease. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: insulin-like growth factor-I; insulin resistance; first-trimester screening; preeclampsia; pregnancy; uterine artery Doppler

INTRODUCTION

Preeclampsia (PE), which affects approximately 2% of pregnancies, is a major cause of maternal and perinatal morbidity and death (ACOG, 2002; Högborg, 2005). The underlying mechanism for PE and fetal growth restriction is thought to be impaired placentation because of inadequate trophoblastic invasion of the maternal spiral arteries, which has been documented by the findings of both histological and Doppler ultrasound studies of the uterine arteries (Khong *et al.*, 1986; Friedman *et al.*, 1991; Meekins *et al.*, 1994; Yu *et al.*, 2005; Plascencia *et al.*, 2007; Poon *et al.*, 2009).

Insulin-like growth factor-I (IGF-I), a strong mitogen that promotes cell proliferation and differentiation, is thought to play a critical role in mediating fetal and postnatal growth (Monzavi and Cohen, 2002; Randhawa and Cohen, 2005). IGF-I is present in almost all cell types of the placenta from the sixth week of gestation and appears to be involved in

many aspects of placental development and function (Han *et al.*, 1996; Forbes and Westwood, 2008). It regulates the differentiation of cytotrophoblasts into syncytiotrophoblast and extravillous trophoblasts, an important function for successful placental development (Milio *et al.*, 1994; Aplin *et al.*, 2000; Lacey *et al.*, 2002; Forbes and Westwood, 2008). In addition, IGF-I enhances the proliferation and survival of placental fibroblast and trophoblasts and rescues them from apoptosis (Smith *et al.*, 2002). IGF-I, as other members of the IGF axis, 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). 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 IGF-I are altered. However, there is conflicting evidence as to whether the levels of these proteins increased or decreased in PE (Table 1).

The aims of our study were first, to investigate the maternal serum concentration of IGF-I at 11–13 weeks in pregnancies that subsequently develop PE and second, to examine the possible association with uterine artery PI, which provides a measure of placental perfusion (Plascencia *et al.*, 2007; Poon *et al.*, 2009).

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Table 1—Studies reporting maternal circulating insulin-like growth factor-I levels (ng/mL) in patients during or before preeclampsia compared to unaffected controls

Author	Gestational age (week)	Unaffected		Preeclampsia	
		<i>n</i>	IGF-I	<i>n</i>	IGF-I
<i>During preeclampsia</i>					
Halhali <i>et al.</i> (1995) ^a	26–40	26	41	26	26*
Giudice <i>et al.</i> (1997)	20–34	29	179	16	81*
Lewitt <i>et al.</i> (1998)	26–39	11	457	10	368*
Halhali <i>et al.</i> (2000)	38–41	24	383	24	265*
Sowers <i>et al.</i> (2001)	Third trimester	805	294	64	352*
Bartha <i>et al.</i> (2002)	28–40	20	235	20	218
Altinkaynak <i>et al.</i> (2003) ^a	27–40	27	35	41	12*
Ingec <i>et al.</i> (2004)	28–40	20	802	60	509*
Kocyigit <i>et al.</i> (2004)	Third trimester	20	114	53	80*
<i>Before preeclampsia</i>					
Grobman and Kazer (2001)	14–28	24	148	12	227*
Sowers <i>et al.</i> (2001)	First trimester	805	206	64	202
Sowers <i>et al.</i> (2001)	Second trimester	805	222	64	254*
Hübinette <i>et al.</i> (2003)	17	127	86	29	101
Hübinette <i>et al.</i> (2003)	33	126	211	23	229
Ning <i>et al.</i> (2004) ^b	8–16	477	0.94	53	0.77*

In all the studies, the mean IGF-I values are given except in Ning *et al.* (2004) in which the median is given.

^a IGF-I levels have been expressed as nmol/L.

^b Free IGF-I in maternal circulation has been studied.

Significance level * $p < 0.05$.

MATERIALS AND METHODS

Study population

This was a case–control study drawn from a large observational prospective study of hypertensive complications of pregnancy in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. In this visit, which is held at 11⁺⁰–13⁺⁶ weeks of gestation, all women have an ultrasound scan to (1) confirm gestational age from the measurement of the fetal crown-rump length (CRL), (2) diagnose any major fetal abnormalities, and (3) measure fetal nuchal translucency (NT) thickness as part of screening for chromosomal abnormalities. In addition, the maternal serum PAPP-A and free β -hCG are determined and the results are combined with the fetal NT to calculate the pregnancy-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 lowest value (L-PI) (Poon *et al.*, 2009). Written informed consent was obtained from the women who agreed to participate in the study, which was approved by the King's College Hospital Ethics Committee.

Stored maternal serum from 18 cases that developed PE requiring delivery before 34 weeks (early-PE) and 35 cases that developed late-PE was available. 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 were previously thawed and refrozen.

Maternal history

Patients were asked to complete a questionnaire on maternal age, racial origin (White, Black, 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 antihypertensives, 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/or 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 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 IGF-I concentration by a quantitative enzyme linked immunoassay (ELISA) technique using DSL-10-2800 IGF-I non-extraction assay (Diagnostic systems laboratories, Inc. Webster, TX, USA). The lower limit of detection of the assay for IGF-I was 0.01 ng/mL.

Statistical analysis

The following steps were taken for the statistical analysis. First, the distribution of serum IGF-I was made Gaussian by square root (sqrt) transformation and normality was confirmed using Kolmogorov–Smirnov test ($D = 0.08$, $p = 0.08$). The distribution of uterine artery L-PI was made Gaussian after logarithmic transformation. Second, multiple regression analysis was used to determine which of the factors among the maternal and pregnancy characteristics are associated with sqrt IGF-I 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 L-PI was expressed as MoM for gestational age, maternal age, BMI, and racial origin as previously described (Poon *et al.*, 2009). Third, Mann–Whitney *U*-test with *post hoc* Bonferroni correction was used to compare median MoM values of IGF-I and uterine artery L-PI between the outcome groups. Fourth, regression analysis was used to determine the significance of the association of maternal serum IGF-I with uterine artery L-PI in the outcome groups. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

RESULTS

The maternal characteristics of each 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 Black women, more women had PE in their previous pregnancy, were chronic hypertensives on antihypertensive medication and their mother had PE. In the group that developed late-PE compared to the unaffected group, women had a significantly higher BMI, there were more Black women, more women had PE in their previous pregnancy and were chronic hypertensives.

Unaffected group

Multiple regression analysis in the unaffected group demonstrated that for sqrt IGF-I significant independent contribution was provided by racial origin and parity but not by fetal CRL ($p = 0.827$), maternal weight ($p = 0.119$), smoking status ($p = 0.467$), or method of conception ($p = 0.553$):

Expected sqrt IGF-I = 10.05 + (2.65 if of Black racial origin, 0 if any other) + (−1.61 if nulliparous, 0 if parous); $R^2 = 0.083$, $p = 0.004$.

In the unaffected group, there were no significant associations between serum IGF-I and uterine artery L-PI ($p = 0.579$).

Preeclampsia group

In pregnancies that developed early-PE and late-PE, the median serum IGF-I was decreased and uterine artery L-PI was increased (Table 3). In the group that developed PE there were no significant associations between serum IGF-I and uterine artery L-PI ($p = 0.632$). There was a significant association between gestation at delivery and uterine artery L-PI MoM ($r = -0.334$; $p = 0.009$) but not IGF-I MoM ($p = 0.579$).

DISCUSSION

The findings of this study confirm that in pregnancies that develop PE there is impaired placental perfusion evident by increased PI in the uterine arteries from the first trimester and that such impaired perfusion is particularly marked in early-PE. The study also shows that in pregnancies that develop PE, the maternal serum concentration of IGF-I is decreased and this decrease is similar in early-PE and late-PE.

In the unaffected controls, the measured concentration of maternal serum IGF-I was higher in women of Black racial origin and lower in nulliparous women but was not associated significantly with other maternal or fetal characteristics. Consequently, as in the case of uterine artery L-PI the measured concentration of IGF-I must be adjusted for ethnicity and parity before comparing with pathological pregnancies (Poon *et al.*, 2009). Only one of the previous studies on IGF-I made adjustments for confounding factors, including maternal age, ethnic origin, parity, and family history of hypertension (Ning *et al.*, 2004). A longitudinal study of 23 unaffected pregnancies at 8–35 weeks of gestation reported that the maternal serum levels of IGF-I remained stable until 20 weeks and then increased in the third trimester (Olausson *et al.*, 2008). In our study, there was no change in serum IGF-I with fetal CRL within the narrow gestational range of 11–13 weeks.

Most studies examining women with established PE reported lower serum IGF-I levels than in normotensive controls (Halhali *et al.*, 1995; Guidice *et al.*, 1997; Lewitt *et al.*, 1998; Halhali *et al.*, 2000; Altinkaynak *et al.*, 2003; Ingec *et al.*, 2004; Kocyigit *et al.*, 2004).

Table 2—Maternal and pregnancy characteristics in the outcome groups

Maternal and pregnancy characteristics	Unaffected (n = 106)	Early preeclampsia (n = 18)	Late preeclampsia (n = 35)
Maternal age in years, median (IQR)	35.5 (32.4–39.5)	28.4 (23.5–33.3)*	32.6 (29.3–38.3)
Body mass index in kg/m ² , median (IQR)	23.9 (21.5–25.9)	26.3 (21.3–34.0)	27.5 (22.9–32.0)*
Gestation at sampling in days, median (IQR)	90 (87–93)	89 (85–90)	87 (85–91)*
Gestation at delivery in weeks, median (IQR)	281 (273–285)	226 (205–234)*	267 (256–279)*
Birth weight in kg, median (IQR)	3.5 (3.2–3.7)	1.5 (1.1–1.8)*	2.9 (2.5–3.3)*
Racial origin			
White, n (%)	88 (83.0)	8 (44.4)	17 (48.6)
Black, n (%)	11 (10.4)	8 (44.4)*	16 (45.7)*
South Asian, n (%)	2 (1.9)	1 (5.6)	2 (5.7)
East Asian, n (%)	3 (2.8)	0	0
Mixed, n (%)	2 (1.9)	1 (5.6)	0
Parity			
Nulliparous, n (%)	41 (38.7)	8 (44.4)	13 (37.1)
Parous—no previous preeclampsia, n (%)	62 (58.5)	6 (33.3)	19 (54.3)
Parous—previous preeclampsia, n (%)	3 (2.8)	4 (22.3)*	3 (8.6)
History of preeclampsia in the mother, n (%)	4 (3.8)	4 (22.3)*	1 (2.9)
Cigarette smoker, n (%)	7 (6.6)	1 (5.6)	5 (14.3)
Conception			
Spontaneous, n (%)	86 (81.1)	17 (94.4)	33 (94.3)
Assisted, n (%)	20 (18.9)	1 (5.6)	2 (5.7)
Medical history			
None, n (%)	98 (92.5)	13 (72.2)	27 (77.1)
Chronic hypertension, n (%)	0	2 (11.1)*	4 (11.4)*
Diabetes mellitus, n (%)	0	1 (5.6)	0
Thrombophilia, n (%)	3 (2.8)	0	0
Others, n (%)	5 (4.7)	2 (11.1)	4 (11.5)
Medication during pregnancy			
None, n (%)	100 (94.3)	13 (72.2)	30 (85.7)
Antihypertensives, n (%)	0	2 (11.1)*	1 (2.9)
Insulin, n (%)	0	1 (5.6)	0
Aspirin/Heparin, n (%)	3 (2.8)	0	0
Others, n (%)	3 (2.8)	2 (11.1)	4 (11.4)

Comparisons between outcome groups (Chi-square test and Fisher's 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 (interquartile range) for maternal serum insulin-like growth factor-I, pregnancy-associated plasma protein A, and uterine artery lowest pulsatility index in the outcome groups

	Unaffected (n = 106)	Early preeclampsia (n = 18)	Late preeclampsia (n = 35)
Insulin-like growth factor-I, median (IQR)			
MoM	1.04 (0.59–1.49)	0.53 (0.40–0.75)*	0.55 (0.42–0.86)*
ng/mL	104.4 (58.2–134.5)	53.8 (40.6–73.9)	69.9 (41.6–93.8)
Uterine artery lowest pulsatility index, median (IQR)			
MoM	0.97 (0.81–1.22)	1.55 (1.18–1.69)*	1.21 (0.83–1.51)*
Unit	1.30 (1.09–1.62)	2.16 (1.69–2.41)	1.64 (1.20–2.14)

Comparisons between outcome groups by Mann–Whitney *U*-test with *post hoc* Bonferroni correction.
Significance level **p* < 0.025.

Our findings indicate that this decrease in circulating levels of IGF-I is apparent from the first trimester of pregnancy and suggests that altered levels of IGF-I may be implicated in the pathogenesis of PE rather than being a mere consequence of the clinical onset of the disease. Our results are similar to those of Ning *et al.* (2004),

who also made adjustments for confounding factors and measured free IGF-I, rather than total IGF-I. There is no obvious explanation for the findings of other studies that examined women before the clinical onset of the disease and reported that the levels of IGF-I either increased or remained significantly unaltered (Grobman and Kazer,

2001; Sowers *et al.*, 2001; Hübinette *et al.*, 2003). There is also one longitudinal study which reported that in women developing PE, compared to controls, serum IGF-I levels were similar in the first trimester and increased both in the second and third trimesters (Sowers *et al.*, 2001).

There is extensive evidence that the underlying mechanism for early-PE is impaired trophoblastic invasion of the maternal spiral arteries, reduced placental perfusion, and fetal growth restriction (Yu *et al.*, 2005; Plascencia *et al.*, 2007; Poon *et al.*, 2009). This is further reinforced by our findings that in the PE group the uterine artery PI was increased and that there was an inverse relationship between PI and gestation at delivery. There is evidence that IGF-I is involved in the regulation of trophoblast invasion, placental development and function (Milio *et al.*, 1994; Aplin *et al.*, 2000; Fowler *et al.*, 2000; Lacey *et al.*, 2002; Smith *et al.*, 2002; Forbes and Westwood, 2008). However, our findings that there was no significant association between serum IGF-I and uterine artery PI or between serum IGF-I and gestation at delivery in the PE group do not lend support to the hypothesis that the involvement of IGF-I in the pathogenesis of PE is mediated through the effect on placental perfusion and development.

In 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 and impaired glucose and lipid metabolism (Vatten and Skjaerven, 2004; D'Anna *et al.*, 2006; Egbor *et al.*, 2006). Late-PE is associated with impaired glucose tolerance and increased insulin resistance (Kaaaja *et al.*, 1995; Lorentzen *et al.*, 1998; D'Anna *et al.*, 2006). There is evidence that IGF-I acts positively on insulin sensitivity (Clemmons *et al.*, 2000; Bartha *et al.*, 2002; Kazer 2003), and it could therefore be speculated that decreased circulating levels of this factor would lead to increased insulin resistance and predisposition to PE. However, Bartha *et al.* (2002) reported that increased insulin resistance is associated with gestational hypertension rather than PE and that there is no significant correlation between insulin sensitivity index and serum IGF-I levels.

This study has shown that both early-PE and late-PE are associated with a decrease in maternal serum IGF-I that is evident from the first trimester of pregnancy. However, the extent to which this decrease is mediated by different mechanisms depending on the type of PE and the extent to which IGF-I is implicated in the pathogenesis of PE remain to be determined.

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