Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2009;25:320–327
DOI: 10.1159/000235878

Received: April 26, 2009
Accepted: May 28, 2009
Published online: September 22, 2009

Maternal Serum Activin A at 11–13 Weeks of Gestation in Hypertensive Disorders of Pregnancy

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Key Words
Activin A · First-trimester screening · Preeclampsia · Uterine artery Doppler

Abstract
Objectives: To investigate whether the maternal serum concentration of activin A at 11–13 weeks of gestation in pregnancies that subsequently develop hypertensive disorders is different from those with a normal outcome and to examine whether any possible differences are related to uterine artery pulsatility index (PI), serum pregnancy-associated plasma protein A (PAPP-A) and serum tumor necrosis factor-α receptor-1 (TNF-R1). ***Material and Methods:*** Serum activin A, TNF-R1, PAPP-A and uterine artery PI were determined in a case-control study of 126 cases that developed preeclampsia, 88 that developed gestational hypertension and 214 controls. ***Results:*** In preeclampsia, compared to controls, uterine artery PI, serum activin A and serum TNF-R1 were higher and serum PAPP-A was lower. In gestational hypertension, compared to controls, serum activin A was higher but uterine artery PI, serum PAPP-A and serum TNF-R1 were not significantly different. There were no significant associations between serum activin A and either uterine artery PI or serum TNF-R1 in either the hypertensive groups or the controls. ***Discussion:*** The data do not support the hypothesis linking activin A with impaired trophoblastic invasion of the maternal spiral arteries, placental hypoxia and the release of cytokines which in turn cause endothelial dysfunction and the development of the clinical symptoms of the disease.

Introduction

Activin A is a glycoprotein hormone produced by many tissues, but in normal pregnancy the main source is the placenta [1–3]. Several studies have reported that in patients with preeclampsia (PE) there is a 2- to 9-fold increase in the maternal serum activin A concentration (table 1) [4–13]. There is also evidence that increased levels of activin A precede the clinical onset of PE and may be evident from the first trimester of pregnancy [14–22].

The exact function of activin A in pregnancy and its role in the pathogenesis of PE are uncertain. However, PE is associated with impaired trophoblastic invasion of the maternal spiral arteries [23, 24], resulting in placental hypoxia and the release of inflammatory factors which cause endothelial cell activation and damage [25–27]. There is evidence that activin A promotes trophoblastic invasion in early pregnancy [28], and the reported increased maternal serum activin A level in patients with PE may reflect a placental compensatory mechanism to promote trophoblastic invasion in cases where this process is impaired [29]. Secretion of activin A by cytotrophoblasts in vitro is stimulated by the proinflammatory cytokine tumor necrosis factor-α (TNF-α) [30]. The circulating level of TNF-α and that of its soluble receptor-1 (TNF-R1) are also increased both during and several weeks before the onset of PE [31]. There is also evidence that in addition to the placenta another source for the increased circulating activin A levels in PE are peripheral

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Table 1. Studies reporting on the association between maternal serum activin A concentration and PE

Study	Gestation weeks	PE		Controls		p value
		n	activin A	n	activin A	
During PE						
Petraglia et al. [4]	29.0 (25–34)	16	57.4	10	9.2	<0.01
Muttukrishna et al. [5]	29.2 (25–33)	20	38.1	20	4.0	<0.001
Silver et al. [6]	35.5 (25–42)	60	3.0*	60	1.0*	<0.0001
D'Antona et al. [7]	32.0 (26–39)	16	4.6	38	1.0*	<0.001
Yair et al. [8]	36.3 (32–40)	20	445.7	20	133.1	<0.0001
Manuelpillai et al. [9]	34.0 (29–40)	23	3.5*	62	1.0*	<0.0001
Keelan et al. [10]	34.9 (30–38)	22	33.4	22	8.0	<0.001
Florio et al. [11]	31.0 (25–38)	21	2.1*	42	1.0 *	<0.001
Bersinger et al. [12]	31.6 (25–39)	19	32.4	19	3.8	<0.001
Diesch et al. [13]	35.0 (29–41)	34	12.1	44	7.1	<0.001
Before PE						
Grobman et al. [14]	21.7 (14–28)	12	11.3	24	11.1	NS
Davidson et al. [15]	16.6 (15–20)	39	1.6	155	1.4	NS
Florio et al. [16]	24	18	2.7	40	1.8	<0.05
Ong et al. [17]	12.0 (11–13)	131	1.5*	494	1.0*	<0.001
Ay et al. [18]	17.0 (16–18)	14	12.3*	164	1.0*	<0.001
Madazli et al. [19]	23.6 (21–26)	14	26.5	108	8.6	<0.001
Spencer et al. [20]	23.0 (22–24)	24	2.1*	144	1.0*	<0.001
Banzola et al. [21]	13.2 (11–15)	56	1.8*	168	1.0*	<0.001
Spencer et al. [22]	12.0 (11–13)	64	1.2*	240	1.0*	<0.05

All values are in ng/ml unless indicated. Figures marked with an asterisk indicate MoM.

mononuclear cells and endothelium activated by pro-inflammatory cytokines such as TNF-α [32].

Previous studies reported that at 11–13 weeks of gestation in pregnancies that subsequently develop PE, the uterine artery pulsatility index (PI), assessed by Doppler ultrasound, is increased [33] and the maternal serum concentration of pregnancy-associated plasma protein A (PAPP-A), which is thought to be involved in placental growth and development, is reduced [20, 34]. The differences between pregnancies developing PE from controls in uterine artery PI and serum PAPP-A are particularly marked in severe early-onset disease requiring delivery before 34 weeks [33, 34].

The aims of this study were to investigate whether the maternal serum concentration of activin A at 11–13 weeks of gestation in pregnancies that subsequently develop hypertensive disorders is different from those with a normal outcome and to examine whether any possible differences are related to uterine artery PI, serum PAPP-A and serum TNF-R1.

Methods

Study Population

This was a case-control study drawn from a large prospective observational study for 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 firstly confirm gestational age from the measurement of the fetal crown-rump length, secondly diagnose any major fetal abnormalities, and thirdly measure fetal nuchal translucency 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 nuchal translucency to calculate the patient-specific risk for trisomy 21 [35, 36]. We recorded maternal characteristics and medical history, measured the uterine artery PI by transabdominal color Doppler [33], and stored serum at –80°C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

The base cohort study population wherein the present case-control study was nested was examined between March 2006 and March 2007 and constituted 8,234 singleton pregnancies. In 147 (1.8%) cases, there was subsequent development of PE, including 32 that required delivery before 34 weeks (early PE) and 115 with late PE, and 135 (1.6%) who developed gestational hypertension

(GH). In all cases in the base cohort, we recorded the maternal demographic characteristics and medical history and measured uterine artery PI and serum PAPP-A. In addition, we measured maternal serum activin A concentration in a case-control population of 126 cases with PE, including 27 with early PE and 99 with late PE, 88 with GH, and 214 controls. The selection of the specific samples from each group of hypertensive disorders was simply based on availability. The cases and controls were matched for length of storage of their blood samples and none of the samples were previously thawed and refrozen.

This study is part of a research program on the early prediction of pregnancy complications and the data from some of the patients on individual components of the present study were published previously [31, 33, 34].

Maternal History

Patients were asked to complete a questionnaire on maternal age, racial origin, cigarette smoking during pregnancy, method of conception, medical history, medication, parity, obstetric history and family history of PE in the mother. The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured and the BMI was calculated using the kg/m^2 formula.

Outcome Measures

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy [37]. In GH, the diastolic blood pressure should be 90 mm Hg or more on at least two occasions 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria. In PE, there should be GH with proteinuria of 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-hour collection is available.

Sample Analysis

Duplicate serum samples of 75 μl were used to measure total activin A concentration by a solid-phase sandwich ELISA using Oxford Bio-Innovation total activin A immunoassay kits (Oxford Bio-Innovation Ltd., Bicester, UK). The lower limit of detection of the assay was 0.078 ng/ml and the between-batch imprecision was 15.8% at activin A concentration of 1.13 ng/ml, 8.3% at 1.79 ng/ml and 12.3% at 3.85 ng/ml. All samples were analyzed in duplicate and those with a coefficient of variation exceeding 15% were reanalyzed.

Maternal serum PAPP-A was measured using the DELFIA XPRESS analyzer (PerkinElmer Life and Analytical Sciences, Waltham, Mass., USA). The variation of the DELFIA XPRESS PAPP-A assay was determined in 20 runs with two replicates using this system. The calibration curve of the first run was used as a reference curve during the 14-day period. The intra- and inter-assay variations were 1.2 and 2.1%, respectively, at a PAPP-A concentration of 462 mU/l, 1.4 and 2.3% at 2,124 mU/l and 1.3 and 2.5% at 5,543 mU/l.

The concentration of TNF-R1 was measured using Quantikine® ELISA kits (R&D Systems Inc., Abingdon, UK). Absorbance readings were taken on a Victor 3 plate reader (PerkinElmer Life and Analytical Sciences, Turku, Finland), and TNF-R1 concentrations were determined using MultiCalc software (PerkinElmer Life and Analytical Sciences, Finland). The between-batch imprecision was 11.3% at a TNF-R1 concentration of 162 pg/ml, 5.8% at 741 pg/ml and 5.4% at 1,693 pg/ml. All samples were analyzed in duplicate and those with a coefficient of variation exceeding 10% were reanalyzed.

Statistical Analysis

Maternal history, uterine artery PI, and PAPP-A were recorded in all cases in the base cohort but activin A and TNF-R1 were measured only in the case-control population.

Comparisons between base-cohort and case-control populations were made by χ^2 or Fisher exact test for categorical variables and by Mann-Whitney test for continuous variables. Comparisons between outcome groups in the case-control study were made by χ^2 or Fisher exact test for categorical variables and by Kruskall-Wallis test and Dunn's procedure for continuous variables.

The distributions of uterine artery PI, PAPP-A, TNF-R1 and activin A were made Gaussian after logarithmic transformation. Distributions were confirmed to be Gaussian using probability plots and Kolmogorov-Smirnov test. Multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of log activin A in the unaffected group. Then the distribution of log activin A, expressed as multiples of the median (MoM) of the unaffected group, were determined in the PE and GH groups of the case-control population. The measured uterine artery PI, PAPP-A and TNF-R1 were converted into MoMs after adjustment for gestation and maternal characteristics as previously described [31, 33, 38]. Logistic regression analysis was used to determine which of the factors amongst the maternal characteristics, log uterine artery PI MoM, log activin A MoM and log PAPP-A MoM had a significant contribution in predicting early PE, late PE and GH. The detection and false positive rates were calculated as the respective proportions of PE or GH (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.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA), Medcalc for Windows, version 9.6.2.0 (MedCalc Software, Mariakerke, Belgium) and XLSTAT-Pro 2008 (Addinsoft, New York, N.Y., USA) were used for data analyses.

Results

The maternal characteristics of each of the outcome groups are compared in table 2.

Unaffected Group

Multiple regression analysis in the unaffected group demonstrated that for log activin A significant independent contributions were provided by maternal weight and racial origin: log expected activin A = 0.455 – 0.003 × maternal weight in kg + (0.082 if Black, 0 if other racial origins); $R^2 = 0.068$, $p = 0.001$.

Multiple regression analysis in the unaffected group demonstrated that for log TNF-R1 significant independent contributions were provided by maternal weight and

Table 2. Maternal characteristics in the three outcome groups

	Unaffected (n = 214)	PE (n = 126)	GH (n = 88)
Median maternal age, years	32.0 (28.7–35.4)	31.6 (26.7–36.3)	33.3 (30.1–35.8)
Median BMI	25.2 (23.0–29.1)	27.0 (23.8–32.0)*	26.5 (24.2–31.0)
Median crown-rump length, mm	64.2 (59.7–71.0)	62.6 (57.9–70.7)	62.5 (57.7–69.0)
Racial origin			
White	150 (70.1)	52 (41.3)	67 (76.1)
Black	43 (20.1)	54 (42.9)*	16 (18.2)
Others	21 (9.8)	20 (15.8)	5 (5.6)
Parity			
Nulliparous	85 (39.7)	78 (61.9)	49 (55.7)
Parous – no previous PE	123 (57.5)	29 (23.0)*	29 (33.0)*
Parous – previous PE	6 (2.8)	19 (15.1)*	10 (11.4)
Cigarette smoker	16 (7.5)	6 (4.8)	7 (8.0)
Family history of PE – mother	7 (3.3)	15 (11.9)*	9 (10.2)*
Conception			
Spontaneous	207 (96.7)	118 (93.7)	85 (96.6)
Assisted	7 (3.3)	8 (6.4)	3 (3.4)
Medical history			
None	207 (96.7)	115 (91.3)	85 (96.6)
Chronic hypertension	1 (0.5)	8 (6.3)*	0
Diabetes mellitus	2 (0.9)	1 (0.8)	2 (2.3)
Others	4 (1.9)	2 (1.6)	1 (1.1)
Medication during pregnancy			
None	194 (90.7)	113 (89.7)	76 (86.4)
Antihypertensives	0	4 (3.2)*	0
Insulin	2 (0.9)	1 (0.8)	2 (2.3)
Others	18 (8.4)	8 (6.3)	10 (11.3)

Figures in parentheses indicate interquartile range or percentages. Comparisons between each outcome group and unaffected controls (χ^2 test and Fisher's exact test for categorical variables and Kruskall-Wallis test and Dunn's procedure for continuous variables). * $p < 0.05$.

Table 3. Median (interquartile range) uterine artery PI, PAPP-A and activin A in the three outcome groups of the cohort and case control

	Unaffected (n = 214)	PE (n = 126)	GH (n = 88)
Uterine artery PI			
MoM	1.05 (0.84–1.30)	1.32 (0.99–1.56)*	1.12 (0.90–1.33)
Unit	1.68 (1.33–2.05)	2.13 (1.57–2.50)	1.76 (1.42–2.07)
Serum PAPP-A			
MoM	1.03 (0.70–1.45)	0.81 (0.53–1.25)*	0.90 (0.62–1.44)
mU/l	2.83 (1.82–4.66)	2.63 (1.38–4.03)	2.03 (1.54–3.49)
Serum TNF-R1			
MoM	1.00 (0.87–1.13)	1.09 (0.94–1.20)*	1.02 (0.95–1.15)
pg/ml	1,169 (1,013–1,297)	1,272 (1,081–1,404)	1,203 (1,112–1,400)
Serum activin A			
MoM	1.00 (0.76–1.28)	1.27 (0.96–1.68)*	1.15 (0.89–1.49)*
ng/ml	1.78 (1.41–2.43)	2.33 (1.82–3.01)	2.05 (1.50–2.70)

Comparisons between outcome groups in the case-control study by Kruskall-Wallis test and Dunn's procedure. * $p < 0.05$.

Table 4. Associations between log activin A MoM with log uterine artery PI MoM, log PAPP-A MoM and log TNF-R1 MoM within each outcome group

	Uterine artery PI		Serum PAPP-A		Serum TNF-R1	
	r	p	r	p	r	p
Control	–0.025	0.714	0.330	<0.001	0.093	0.176
PE	–0.076	0.400	0.277	0.002	–0.012	0.893
GH	–0.067	0.538	0.388	<0.001	0.105	0.329

racial origin: log expected TNF-R1 = 2.984 + 0.001 × maternal weight in kg + (–0.030 if Black, 0 if other racial origins); $R^2 = 0.051$, p = 0.004.

In each patient, we used these formulae to derive the expected log activin A and log TNF-R1 and then expressed the observed values as MoMs of the expected (table 3). Similarly, we used previously derived formulae for uterine artery PI and PAPP-A to calculate respective MoM values [33, 38].

Hypertensive Disorders

In PE, compared to controls, uterine artery PI, serum activin A and serum TNF-R1 were higher and serum PAPP-A was lower (table 3). In GH, compared to controls, serum activin A was higher but uterine artery PI, serum PAPP-A and serum TNF-R1 were not significantly different.

Relationships between Serum Activin A and the Other Predictors

There were no significant associations between serum activin A and either uterine artery PI or serum TNF-R1 in either the hypertensive groups or in the controls (table 4). In contrast, there were significant associations between serum activin A and serum PAPP-A in both the hypertensive groups and in the controls (table 4; fig. 1).

Screening for Early PE

Logistic regression analysis demonstrated that in the prediction of early PE there were significant contributions from log MoM uterine artery PI (OR $1.7E^5$, 95% CI 247.8–$1.2E^8$; p < 0.0001), log MoM PAPP-A (OR 0.050, 95% CI 0.006–0.426; p = 0.006), and log MoM activin A (OR 164.2, 95% CI 4.6–5,833.8; p = 0.005), history of chronic hypertension (OR 108.0, 95% CI 6.1–1,900.6; p = 0.001), Black ethnic origin (OR 3.6, 95% CI 1.1–12.3; p = 0.041) and parous with no previous PE (OR 0.182, 95% CI 0.049–0.677; p = 0.011) but not log MoM TNF-R1 (p = 0.127), BMI (p = 0.782) or family history of PE (p = 0.305); $R^2 = 0.569$, p < 0.0001.

The estimated detection rate of screening for early PE by activin A was 11.1 and 25.9% at respective false positive rates of 5 and 10%. The performance of screening for early PE by a combination of history, PAPP-A and uterine artery PI (AROC 0.921, 95% CI 0.879–0.952) was not significantly improved by the addition of activin A (AROC 0.927, 95% CI 0.886–0.956, p = 0.787).

Screening for Late PE

Logistic regression analysis demonstrated that in the detection of late PE there were significant contributions from log MoM uterine artery PI (OR 36.0, 95% CI 3.7–346.7; p = 002), log MoM activin A (OR 32.1, 95% CI 6.0–171.7; p < 0.001), BMI (OR 1.1, 95% CI 1.0–1.2; p = 0.002), Black ethnic origin (OR 3.4, 95% CI 1.8–6.4; p < 0.001), parous with no previous PE (OR 0.171, 95% CI 0.09–0.324; p < 0.001) and family history of PE (OR 4.5, 95% CI 1.4–14.7; p = 0.014), but not log MoM PAPP-A (p = 0.114) or history of chronic hypertension (p = 0.215) or log MoM TNF-R1 (p = 0.121); $R^2 = 0.382$, p < 0.0001.

The estimated detection rate of screening for late PE by activin A was 15.3 and 25.5% at respective false positive rates of 5 and 10%. The performance of screening for late PE by a combination of history and uterine artery PI (AROC 0.806, 95% CI 0.758–0.848) was not significantly improved by the addition of activin A (AROC 0.816, 95% CI 0.768–0.857; p = 0.593).

Screening for GH

Logistic regression analysis demonstrated that in the detection of GH there were significant contributions from log MoM activin A (OR 7.7, 95% CI 1.7–35.6; p = 0.009), BMI (OR 1.1, 95% CI 1.0–1.1; p = 0.002), parous with no previous PE (OR 0.319, 95% CI 0.182–0.557; p < 0.001) and family history of PE (OR 3.4, 95% CI 1.1–10.3; p = 0.035), but not log MoM PAPP-A (p = 0.490), log MoM uterine artery PI (p = 0.079) or log MoM TNF-R1 (p = 0.183) or ethnic origin (p = 0.242); $R^2 = 0.168$, p < 0.0001.

The estimated detection rate of screening for GH by activin A was 6.8 and 14.8% at respective false positive

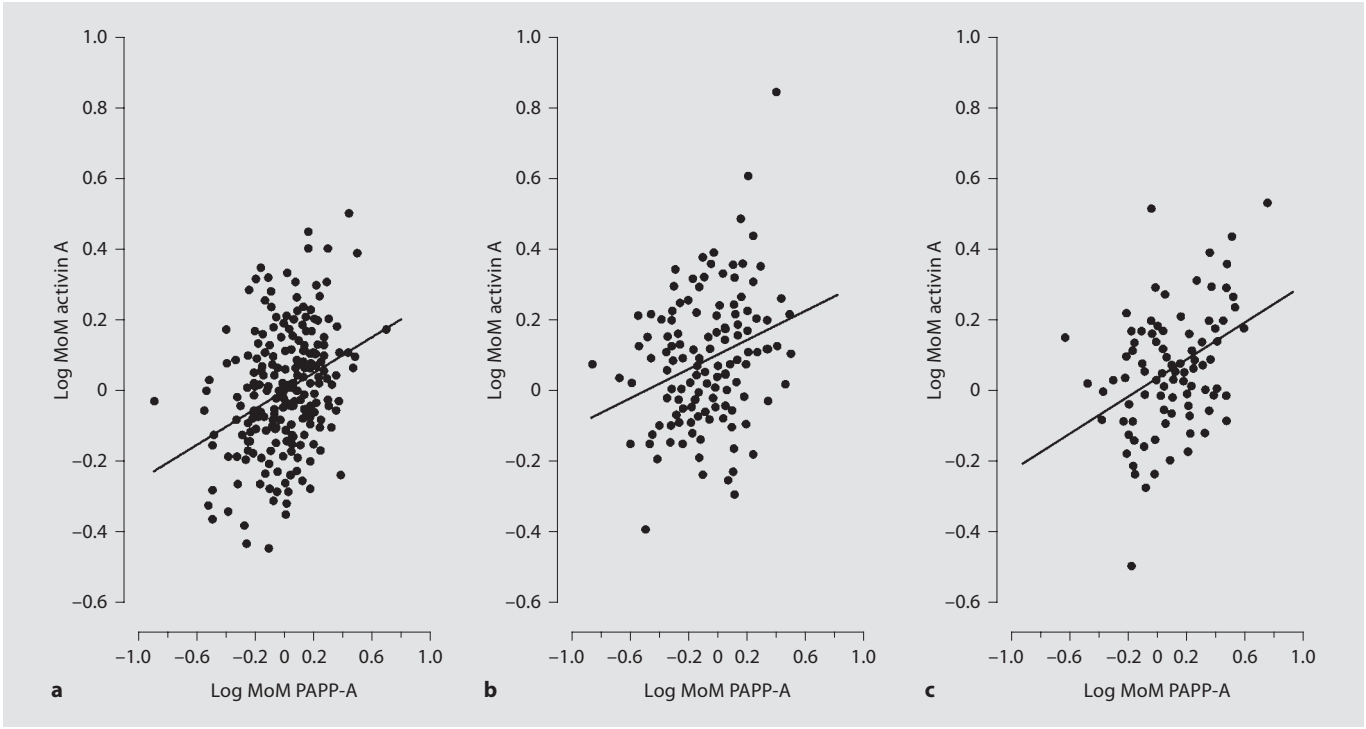

Fig. 1. Relationship between maternal serum activin A and PAPP-A in unaffected pregnancies (**a**), those that subsequently developed PE (**b**) and GH (**c**).

rates of 5 and 10%. The performance of screening for GH by history (AROC 0.697, 95% CI 0.642–0.749) was not significantly improved by the addition of activin A (AROC 0.704, 95% CI 0.649–0.755).

Discussion

The data of this study demonstrate that at 11–13 weeks of gestation women who subsequently develop PE have increased maternal serum levels of activin A and TNF-R1, reduced serum PAPP-A and increased uterine artery PI. Increased serum activin A was also observed in pregnancies developing GH. However, the increased activin A in PE was not associated with either uterine artery PI or serum TNF-R1.

In the unaffected controls, the measured concentration of maternal serum activin A decreased with maternal weight and was higher in Black than in White women. Consequently, as in the case of serum PAPP-A and uterine artery PI, the measured concentration of activin A must be adjusted for these variables before comparing with pathological pregnancies.

The finding of increased serum activin A concentration in the first trimester in pregnancies that subsequently develop PE provides some evidence for the involvement of this hormone in the pathogenesis of the disease. However, there was no significant association between serum activin A and uterine artery PI or TNF-R1 in either the PE or the unaffected group. Consequently, our results do not provide support for the hypothesis linking activin A with impaired trophoblastic invasion of the maternal spiral arteries, placental hypoxia and the release of cytokines which in turn cause endothelial dysfunction and the development of the clinical symptoms of the disease. This is true irrespective of whether the source for the elevated activin A in maternal serum is the placenta or the activated maternal endothelium and monocytes [29, 32].

Another early marker of subsequent development of PE is low maternal serum concentration of PAPP-A. This is a syncytiotrophoblast-derived metalloproteinase which enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins [39, 40]. The insulin-like growth factor system is believed to play an important role in placental growth and development [41]. There was a significant association between serum

activin A and PAPP-A in both the PE and unaffected groups. However, contrary to what would be expected from the finding that in PE serum activin A is increased and PAPP-A is decreased, the relation between the two was not inverse. Consequently, the mechanism for the early increase in serum activin A in pregnancies destined to develop PE and the involvement of this hormone in the pathogenesis of the disease remain uncertain.

Serum activin A at 11–13 weeks was increased both in pregnancies developing PE and to a lesser degree in those developing GH. Previous studies in patients with established disease reported contradictory results. Petraglia et al. [42] reported that in patients with PE but not in those with GH serum activin A levels were significantly higher than in normotensive controls. In contrast, Silver et al. [6] also examined women with PE, GH and normotensive controls and reported that the median value was 1.0 MoM in controls, 2.0 MoM in GH and 3.0 MoM in PE. Muttukrishna et al. [43] measured serum activin A longitudinally during pregnancy and reported that during the third trimester the levels were significantly increased in both those developing PE and GH, but in the second trimester increased levels were observed only in the PE group. The possibility of different mechanisms underlying the increased serum activin A concentration in PE and GH was raised by a study investigating the effect of treating hypertension in such patients by α-methyldopa [44]. At presentation, serum activin A was increased in the PE and to a lesser degree in the GH groups but within 48 h of antihypertensive treatment and similar effect on blood pressure there was a significant decrease in activin A levels only in the PE group.

Previous studies examining the potential performance of serum activin A in screening for PE are confined to the second trimester. Muttukrishna et al. [43] reported that at 21–25 weeks serum activin A was above the 90th and 95th percentiles in 59 and 38%, respectively, of cases that subsequently developed PE. Florio et al. [16] estimated that screening for PE by activin A at 24 weeks would have a detection rate of 61% at a false positive rate of 11%. Spencer et al. [20, 22] estimated that screening for PE by a combination of uterine artery PI at 22–24 weeks and serum activin A either at 22–24 weeks or at 11–13 weeks would have a detection rate of about 60% at a false positive rate of 5%. In our study, serum activin A above the 95th percentile was observed only in 11.1, 15.3, and 6.8% of patients developing early PE, late PE and GH, respectively, and inclusion of this metabolite in first-trimester screening for hypertensive disorders does not improve the prediction provided by maternal history, uterine artery Doppler and serum PAPP-A.

In pregnancies that subsequently develop hypertensive disorders, the maternal serum activin A concentration at 11–13 weeks of gestation is increased but the underlying mechanism for such increase is uncertain.

Acknowledgments

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No. 1037116). The assays were sponsored by PerkinElmer, Inc., Wallac Oy, Turku, Finland. The assays were performed by the NIHR Cambridge Biomedical Research Centre, Core Biochemical Assay Laboratory, Addenbrookes NHS Trust, Cambridge, UK.

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