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First-trimester maternal serum tumor necrosis factor receptor-1 and pre-eclampsia

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KEYWORDS: Doppler; first-trimester screening; pre-eclampsia; tumor necrosis factor; uterine artery

ABSTRACT

Objectives *To examine whether the maternal serum concentration of the soluble receptor-1 of tumor necrosis factor-α (TNF-R1) at 11–13 weeks of gestation in pregnancies that subsequently develop pre-eclampsia is different from that in women without this complication.*

Methods *The concentration of TNF-R1 at 11 + 0 to 13 + 6 weeks was measured in samples from 128 cases that subsequently developed pre-eclampsia and 569 controls with no pregnancy complications. TNF-R1 and uterine artery pulsatility index (UtA-PI) values were expressed as multiples of the median (MoM) adjusted for maternal factors. The distributions of log TNF-R1 MoM and log UtA-PI MoM in the control and pre-eclampsia groups were compared. Logistic regression analysis was used to determine whether a significant contribution is provided by maternal factors, TNF-R1 and UtA-PI in predicting pre-eclampsia. The performance of screening was determined by analysis of receiver–operating characteristics curves.*

Results *Median TNF-R1 and UtA-PI were significantly higher in the pre-eclampsia group (TNF-R1, 1.062 MoM; UtA-PI, 1.301 MoM) than in the control group (TNF-R1, 0.996 MoM; UtA-PI, 1.037 MoM). There was no significant association between TNF-R1 and gestational age at delivery, birth weight percentile or UtA-PI. Logistic regression analysis demonstrated significant contributions to the detection of pre-eclampsia from maternal factors and UtA-PI but not from TNF-R1.*

Conclusions *In pregnancies developing pre-eclampsia the maternal serum TNF-R1 concentration at 11–13 weeks of gestation is increased, but the level of TNF-R1 is not associated with the degree of impairment in placental perfusion or the severity of pre-eclampsia. Measurement of serum TNF-R1 does not improve the prediction of pre-eclampsia provided by screening based on a combination of maternal factors and UtA-PI.*

INTRODUCTION

Pre-eclampsia, which is an important cause of maternal and perinatal mortality and morbidity, is thought to be the consequence of impaired trophoblastic invasion of the maternal spiral arteries[1–6]. This leads to placental hypoxia and the release of inflammatory factors that cause endothelial cell activation and damage[7–9]. Cytokines are involved in fetoplacental development, and have been suggested to be the placental factor capable of damaging endothelial cells and contributing to many of the pathophysiological changes associated with pre-eclampsia[10–12].

Several studies have reported that the maternal serum concentration of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and its soluble receptor-1 (TNF-R1) are significantly higher in patients with pre-eclampsia than in normotensive controls (Table 1)[12–22]. However, there is controversy about whether the altered levels precede the onset of the disease. Some studies have reported increased TNF-α or TNF-R1 from as early as the first trimester in patients who subsequently develop pre-eclampsia, whereas others found no significant difference from controls (Table 1)[13,22–24].

Doppler studies of the maternal uterine arteries (UtAs) at 11–13 weeks of gestation have demonstrated that in pregnancies that subsequently develop pre-eclampsia the pulsatility index (PI) is increased, and this is particularly marked in severe early-onset disease requiring delivery before 34 weeks[25].

The aim of this study was to investigate whether the maternal serum concentration of TNF-R1 at 11–13 weeks of gestation in pregnancies that subsequently develop pre-eclampsia is different from that in women without this complication, and whether any possible differences

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Table 1 Studies comparing maternal serum concentration of tumor necrosis factor-α (TNF-α) and its soluble receptor-1 (TNF-R1) in pregnancies with pre-eclampsia and normotensive controls

		Pre-eclampsia		*Metabolite concentration*		
Reference	*Metabolite*	n	*Gestation (weeks)*	*Pre-eclampsia*	*Control*	P
Studies during pre-eclampsia						
Kupferminc *et al.* 1994[12]	TNF-α (pg/mL)	16	> 28	35 (0–160)	0 (0–60)	< 0.05
Serin *et al.* 2002[13]	TNF-α (pg/mL)	10	26–35	11.1 ± 1.4	9.2 ± 0.8	< 0.05
Velzing-Aarts *et al.* 2002[14]	TNF-α (pg/mL)	13	33.4 ± 4.5	42 (16–95)	27 (9–34)	< 0.01
Vince *et al.* 1995[15]	TNF-R1 (ng/mL)	31	32.7 ± 2.57	1.22 (0.51–7.65)	0.71 (0–1.36)	< 0.001
Williams *et al.* 1998[16]	TNF-R1 (ng/mL)	138	36.4 ± 3.8	1.69 ± 1.02	1.35 ± 1.01	< 0.05
Sanchez *et al.* 2000[17]	TNF-R1 (ng/mL)	125	36.0 ± 0.3	0.92 ± 0.03	0.69 ± 0.02	< 0.001
Nunez-Gonzalez *et al.* 2001[18]	TNF-R1 (ng/mL)	15	36.07 ± 0.82	5.18 ± 0.54	2.69 ± 0.17	< 0.001
Bowen *et al.* 2001[19]	TNF-R1 (ng/mL)	21	37 ± 0.4	1.93 ± 0.12	1.96 ± 0.11	NS
Visser *et al.* 2002[20]	TNF-R1 (ng/mL)	21	31 (26–36)	3.99 (2.14–6.09)	1.67 (1.29–2.26)	< 0.001
Madazli *et al.* 2003[21]	TNF-R1 (ng/mL)	35	34.2 ± 3.7	0.71 ± 0.06	0.54 ± 0.04	< 0.001
Schipper *et al.* 2005[22]	TNF-R1 (ng/mL)	24	30–34	1.46 ± 0.26	1.43 ± 0.29	NS
Studies before pre-eclampsia						
Hamai *et al.* 1997[23]	TNF-α (pg/mL)	8	11–13	9.5 (3.2–15.8)	4.5 (1.9–7.1)	< 0.05
Serin *et al.* 2002[13]	TNF-α (pg/mL)	10	9–17	8.9 ± 0.9	9.1 ± 1.2	NS
	TNF-α (pg/mL)	10	18–25	8.8 ± 0.5	9.2 ± 1.2	NS
Williams *et al.* 1999[24]	TNF-R1 (ng/mL)	35	15–22	0.72 ± 0.19	0.63 ± 0.16	0.003
Schipper *et al.* 2005[22]	TNF-R1 (ng/mL)	29	7–16	1.16 ± 0.22	1.16 ± 0.30	NS
	TNF-R1 (ng/mL)	27	19–25	1.21 ± 0.21	1.28 ± 0.26	NS

Values are mean ± SD, range or median (range). NS, not significant.

are related to the severity of pre-eclampsia and Doppler evidence of impaired placental perfusion.

METHODS

Study population

This was a case–control study. In our center we performed screening for pre-eclampsia in women attending for routine assessment of risk for chromosomal abnormalities by measurement of fetal nuchal translucency thickness, and maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A at 11 + 0 to 13 + 6 weeks of gestation[26]. We recorded maternal characteristics and medical history, measured the UtA-PI by transabdominal color Doppler imaging[25] 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.

In this study we measured TNF-R1 in samples from 128 cases with pre-eclampsia, including 29 requiring delivery before 34 weeks of gestation (early pre-eclampsia), 88 with gestational hypertension, 296 with small-for-gestational age (SGA) neonates and 57 with spontaneous preterm delivery before 34 weeks of gestation. Each case was matched with one control case that had blood collected and stored on the same day, did not develop any pregnancy complications and resulted in the live birth of phenotypically normal neonates.

Maternal history

Patients were asked to complete a questionnaire on maternal age, racial origin (white, black, Indian or Pakistani, Chinese or Japanese and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous, use of ovulation drugs or *in-vitro* fertilization (IVF)), medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome, thrombophilia, human immunodeficiency virus infection and sickle cell disease), medication (including antihypertensive, antidepressant, antiepileptic, anti-inflammatory, aspirin, β-mimetic, insulin, steroids, thyroxine), parity (parous or nulliparous if no delivery beyond 23 weeks), obstetric history (including previous pregnancy with pre-eclampsia or spontaneous preterm delivery before 34 weeks) and family history of pre-eclampsia (mother). The maternal weight and height were measured, and the body mass index (BMI) was calculated.

Outcome measures

The definitions of pre-eclampsia and gestational hypertension were those of the International Society for the Study of Hypertension in Pregnancy[27]. In gestational hypertension the diastolic blood pressure should be ≥ 90 mmHg 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 pre-eclampsia there should be gestational hypertension with proteinuria of ≥ 300 mg 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 pre-eclampsia superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (a 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).

The newborn was considered to be SGA if the birth weight was less than the 5th percentile after correction for gestational age at delivery and sex, maternal racial origin, weight, height and parity[28].

Sample analysis

The concentration of TNF-R1 was measured using Quantikine® ELISA kits (R&D Systems Inc., Abingdon, UK) and the assay was performed according the manufacturer's instructions. Quality control samples were prepared using serum from women in the second trimester of pregnancy. All patient and quality control samples were prediluted 1 in 10 in Calibrator Diluent RD60 before analysis. Sampling, reagent addition and plate washing was performed on a Dade Behring BEP2000 analyzer (Liederbach, Germany). Addition of substrate and stop solution was performed manually. 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). The results were multiplied by 10 to compensate for the sample predilution step. All samples were analyzed in duplicate and those with a coefficient of variation exceeding 10% were reanalyzed (73 of the 1138 samples). The between-batch coefficients of variation were 11.3% at a TNF-R1 concentration of 162 pg/mL, 5.8% at 741 pg/mL and 5.4% at 1693 pg/mL.

Statistical analysis

The measured concentration of TNF-R1 was log transformed to make the distribution Gaussian. Multiple regression analysis was then used to determine which of the factors shown in Table 2 were significant predictors of log TNF-R1 in the control group, and from the regression model the value in each case and control was expressed as a multiple of the expected median (MoM) in the control group. The Mann–Whitney *U*-test was used to determine the significance of differences in the median MoM between each pregnancy complication group and controls.

In each case and control the measured UtA-PI was converted into a MoM after adjustment for gestational age, maternal age, racial origin, BMI and previous history of pre-eclampsia, as described previously[29]. Linear regression analysis was then used to determine the significance of the association between log TNF-R1 MoM and log UtA-PI MoM in each outcome group.

Logistic regression analysis was used to determine which of the factors maternal characteristics, log TNF-R1 MoM and log UtA-PI MoM had a significant contribution in predicting pre-eclampsia. The performance of screening was determined by analysis of receiver–operating characteristics (ROC) curves. The statistical software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

RESULTS

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

Multiple regression analysis in the control group demonstrated that significant independent contributions to log TNF-R1 were provided by racial origin, BMI and method of conception:

$$\text{Log expected TNF-R1} = 2.998 - 0.003 \times \text{BMI in kg/m}^2 + (-0.042 \text{ if black}, -0.033 \text{ if Indian or Pakistani}, 0 \text{ if other racial origins}) + (0.080 \text{ if conceived by IVF}, 0 \text{ if conceived spontaneously or by use of ovulation drugs}); R^2=0.061, P < 0.0001.$$

In each patient we used this formula to derive the expected log TNF-R1 and then expressed the observed value as a MoM of the expected value.

The median TNF-R1 MoM and UtA-PI MoM were significantly higher in the pre-eclampsia and SGA groups than in the control group, but there were no significant differences between the gestational hypertension and preterm delivery groups compared with controls (Table 3).

In the pre-eclampsia group there was no significant association between log TNF-R1 MoM and gestational age at delivery ($P = 0.07$) (Figure 1), birth weight percentile ($P = 0.44$) or log UtA-PI MoM ($P = 0.81$). Among patients with pre-eclampsia, UtA-PI MoM was significantly higher in the group with severe early disease requiring delivery before 34 weeks than in those delivering at 34 weeks or later ($P < 0.0001$) but there was no such significant difference for TNF-R1 MoM ($P = 0.822$). In the SGA group there was no significant association between log TNF-R1 MoM and birth weight percentile ($P = 0.63$) or log UtA-PI MoM ($P = 0.20$).

Patient-specific risks for pre-eclampsia and small-for-gestational age neonate

The patient-specific risks for pre-eclampsia and SGA (%) were calculated from the formula:

$$\text{Odds}/(1 + \text{odds})$$

where odds = e^Y. Y was derived from logistic regression analysis.

Regression analysis demonstrated significant contributions to the detection of pre-eclampsia from maternal factors, TNF-R1 and UtA-PI, but in multiple regression analysis there was no significant contribution from TNF-R1 ($P = 0.07$) to the prediction provided by maternal factors and UtA-PI:

$$Y = -4.586 + 4.763 \times \text{log UtA-PI MoM} + (1.153 \text{ if family history of pre-eclampsia}) + (1.313 \text{ if black}, 1.050 \text{ if Indian or Pakistani}, 0 \text{ if other racial origins}) + 0.106 \times \text{BMI in kg/m}^2 + (0 \text{ if nulliparous or parous with previous}$$

Table 2 Maternal characteristics in the five outcome groups

Maternal characteristic	*Control (n = 569)*	*Pre-eclampsia (n = 128)*	*Gestational hypertension (n = 88)*	*Small-for-gestational age (n = 296)*	*Preterm delivery (n = 57)*
Maternal age (years)	32.6 (16–45)	31.6 (17–49)	33.3 (18–46)	32.2 (17–44)	33.2 (18–46)
Body mass index (kg/m^2)	24.6 (17.4–46.7)	27.1 (18.9–46.4)‡	26.5 (19.6–53.9)‡	24.5 (17.3–43.1)	25.1 (19.1–51.9)
Crown–rump length (mm)	64.0 (45–84)	62.3 (46–84)	62.5 (47–83)	61.6 (46–84)‡	64.1 (47–84)
Racial groups					
White	410 (72.1)	53 (41.4)‡	67 (76.1)	206 (69.6)	42 (73.7)
Black	95 (16.7)	55 (43.0)‡	16 (18.2)	57 (19.3)	11 (19.3)
Indian or Pakistani	31 (5.4)	9 (7.0)	0 (0)*	17 (5.7)	4 (7.0)
Chinese or Japanese	12 (2.1)	2 (1.6)	1 (1.1)	1 (0.3)*	0 (0)
Mixed	21 (3.7)	9 (7.0)	4 (4.5)	15 (5.1)	0 (0)
Parity					
Nulliparous	266 (46.7)	79 (61.7)†	49 (55.7)	152 (51.4)	24 (42.1)
Parous – no previous pre-eclampsia	287 (50.4)	30 (23.4)‡	29 (33.0)†	134 (45.3)	29 (50.9)
Parous – previous pre-eclampsia	16 (2.8)	19 (14.8)‡	10 (11.4)*	10 (3.4)	4 (7.0)
Parous – previous spontaneous preterm delivery	3 (0.5)	0 (0)	2 (2.3)	5 (1.7)	6 (10.5)‡
Cigarette smoker	25 (4.4)	6 (4.7)	7 (8.0)	53 (17.9)‡	7 (12.3)*
Family history of pre-eclampsia – mother	22 (3.9)	15 (11.7)†	9 (10.2)*	10 (3.4)	1 (1.8)
Conception					
Spontaneous	554 (97.4)	120 (93.8)	85 (96.6)	284 (95.9)	55 (96.5)
Ovulation drugs	10 (1.8)	6 (4.7)	0 (0)	7 (2.4)	0 (0)
In-vitro fertilization	5 (0.9)	2 (1.6)	3 (3.4)	5 (1.7)	2 (3.5)
Medical history					
None	559 (98.2)	117 (91.4)‡	85 (96.6)	283 (95.6)†	50 (87.7)‡
Chronic hypertension	1 (0.2)	8 (6.3)‡	0 (0)	10 (3.4)‡	1 (1.8)
Diabetes mellitus	4 (0.7)	1 (0.8)	2 (2.3)	3 (1.0)	5 (8.8)‡
Antiphospholipid syndrome	3 (0.5)	1 (0.8)	1 (1.1)	0 (0)	1 (1.8)
Thrombophilia	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)
Sickle cell disease	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Human immunodeficiency viral infection	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Medication during pregnancy					
None	533 (93.7)	115 (89.8)	76 (86.4)*	258 (87.2)‡	50 (87.7)
Antihypertensives	0 (0)	4 (3.1)*	0 (0)	7 (2.4)‡	0 (0)
Insulin	3 (0.5)	1 (0.8)	2 (2.3)	3 (1.0)	4 (7.0)†
Steroids	1 (0.2)	0 (0)	0 (0)	1 (0.3)	0 (0)
β-mimetics	10 (1.8)	4 (3.1)	4 (4.5)	17 (5.7)	0 (0)
Thyroxine	9 (1.6)	2 (1.6)	2 (2.3)	4 (1.4)	1 (1.8)
Aspirin	3 (0.5)	0 (0)	2 (2.3)	0 (0)	0 (0)
Antiepileptic	2 (0.4)	1 (0.8)	1 (1.1)	1 (0.3)	2 (3.5)
Antidepressants	6 (1.1)	1 (0.8)	1 (1.1)	3 (1.0)	0 (0)
Anti-inflammatory	2 (0.4)	0 (0)	0 (0)	2 (0.7)	0 (0)

Values are median (range) or *n* (%). *$P < 0.05$, †$P < 0.01$, ‡$P < 0.0001$ vs. control (unaffected) group (chi-square test or Fisher's exact test for categorical variables; *t*-test for continuous variables).

Table 3 Comparison of tumor necrosis factor receptor-1 and uterine artery pulsatility index of each adverse outcome group with controls

	Tumor necrosis factor receptor-1		*Uterine artery pulsatility index*	
Outcome group	*MoM (Median (IQR))*	P*	*MoM (Median (IQR))*	P*
Control	0.996 (0.883–1.134)	—	1.037 (0.838–1.248)	—
Pre-eclampsia	1.062 (0.924–1.218)	0.004	1.301 (0.984–1.542)	< 0.0001
Gestational hypertension	0.995 (0.932–1.138)	0.207	1.100 (0.885–1.287)	0.107
Small-for-gestational age	1.030 (0.901–1.180)	0.043	1.087 (0.889–1.332)	0.011
Preterm delivery	1.029 (0.921–1.119)	0.246	1.047 (0.780–1.282)	0.848

*Mann–Whitney *U*-test. IQR, interquartile range; MoM, multiples of the median.

pre-eclampsia, −1.447 if parous without previous pre-eclampsia) + (3.062 if history of chronic hypertension); $R^2 = 0.321$, $P < 0.0001$.

Regression analysis demonstrated significant contributions for the detection of SGA from maternal factors, TNF-R1 and UtA-PI, but in multiple regression analysis

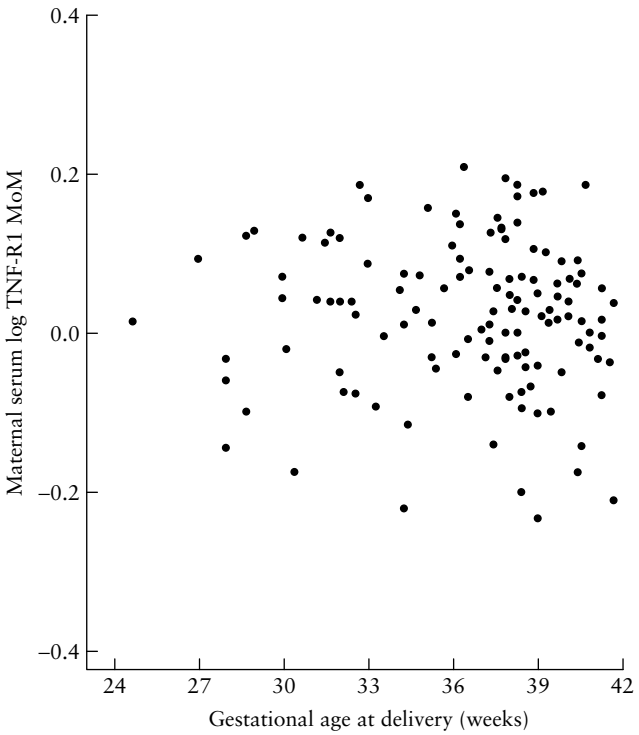

Figure 1 Relationship between tumor necrosis factor receptor-1 (TNF-R1) and gestational age at delivery in the pre-eclampsia group.

there was no significant contribution from TNF-R1 ($P = 0.13$) to the prediction provided by maternal factors and UtA-PI:

$Y = 2.975 + 1.849 \times \log$ UtA-PI MoM $- 0.061 \times$ crown–rump length in mm + (1.705 if smoker, 0 if non-smoker) + (3.257 if history of chronic hypertension) + (1.801 if use of β-mimetic drugs); $R^2 = 0.167$, $P < 0.0001$.

Performance of screening

The areas under the ROC curves and detection rates of pre-eclampsia and SGA for different false-positive rates in screening by maternal factors only, serum TNF-R1 only, UtA-PI only and their combination are summarized in Table 4, and illustrated in Figures 2 and 3. In the prediction of pre-eclampsia, the area under the ROC curve was significantly higher when screening by history with UtA-PI than by history alone ($P = 0.04$). In the prediction of SGA, the area under the ROC curve was not significantly higher when screening by history with UtA-PI than by history alone ($P = 0.19$).

DISCUSSION

The findings of this study demonstrate that the maternal serum TNF-R1 concentration is increased at 11–13 weeks of gestation in pregnancies developing pre-eclampsia. However, the level of TNF-R1 is not significantly associated with the degree of impairment of placental perfusion or the severity of pre-eclampsia, and measurement of serum TNF-R1 does not improve the prediction of pre-eclampsia provided by screening based on a combination of maternal factors and UtA-PI.

The finding of an association between pre-eclampsia and increased maternal serum TNF-R1 is compatible with the results of previous studies. Our results demonstrate that there is evidence of an inflammatory process from as early as the first trimester of pregnancy in women destined to develop pre-eclampsia, which precedes the clinical onset of the disease by several months. However, our results do not provide support for the hypothesis linking impaired trophoblastic invasion of the maternal spiral arteries with placental hypoxia and the release of cytokines, which in turn cause endothelial dysfunction and development of the clinical symptoms of the disease. This is true irrespective of whether the increased concentration of TNF-α in maternal serum is derived from the placenta or other sources such as the maternal endothelium or activated monocytes[30]. Doppler studies assessing placental perfusion have shown that the prevalence of increased UtA-PI in pregnancies developing pre-eclampsia is considerably higher in those developing early-onset disease requiring delivery before 34 weeks than in late-onset disease[25,29]. Similarly, pathological studies have demonstrated that the prevalence of placental lesions in women with pre-eclampsia is inversely related to the gestational age at delivery[31,32]. In contrast, in our patients with pre-eclampsia there was no significant

Table 4 Comparison of performance of screening for pre-eclampsia and small-for-gestational age (SGA) by maternal factors, tumor necrosis factor receptor-1 (TNF-R1), uterine artery pulsatility index (UtA-PI), and their combination

	Mean area under ROC curve (95% CI)		*Detection rate (%) for fixed FPR*			
			Pre-eclampsia		*SGA*	
Screening test	*Pre-eclampsia*	*SGA*	*FPR 5%*	*FPR 10%*	*FPR 5%*	*FPR 10%*
Maternal factors	0.788 (0.755–0.817)	0.687 (0.655–0.718)	29.7	46.1	24.0	34.8
TNF-R1	0.582 (0.544–0.619)	0.542 (0.508–0.575)	10.9	18.8	6.8	12.8
UtA-PI	0.669 (0.633–0.704)	0.552 (0.519–0.586)	21.9	34.4	5.1	16.9
Maternal factors with UtA-PI	0.819 (0.788–0.847)	0.699 (0.667–0.729)	32.0	54.7	23.6	36.5

FPR, false positive rate; ROC, receiver–operating characteristics.

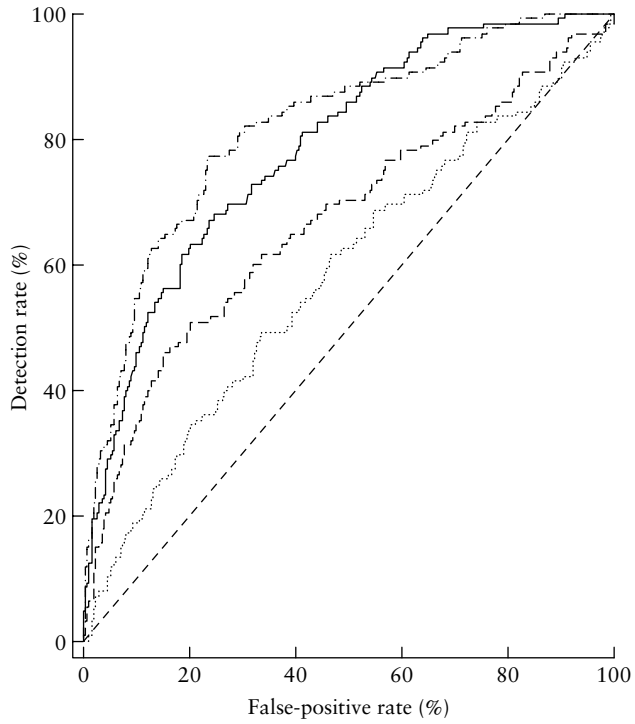

Figure 2 Receiver–operating characteristics curves in the prediction of pre-eclampsia by maternal factors (———), tumor necrosis factor receptor-1 (·····), uterine artery pulsatility index (UtA-PI) (– – – – –), and the combination of UtA-PI and maternal factors (-·-·-·-).

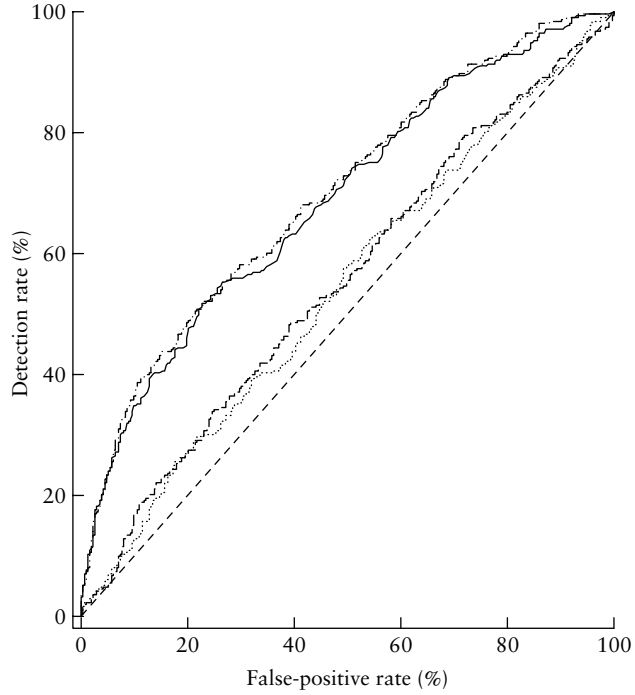

Figure 3 Receiver–operating characteristics curves in the prediction of small-for-gestational age by maternal factors (———), tumor necrosis factor receptor-1 (·····), uterine artery pulsatility index (UtA-PI) (– – – – –), and the combination of UtA-PI and maternal factors (-·-·-·-).

association between the level of TNF-R1 and either UtA-PI or the gestational age at delivery. Consequently, the mechanism underlying the observed association between increased TNF-R1 and the development of pre-eclampsia is uncertain.

In a small number of pregnancies with SGA without pre-eclampsia there was an increase in maternal serum TNF-R1 and UtA-PI. It may be postulated that in these cases the cause of SGA was impaired placentation with consequent placental hypoxia and release of proinflammatory cytokines. However, as in the case of pre-eclampsia, there was no significant association between serum TNF-R1 and UtA-PI. In addition, neither TNF-R1 nor UtA-PI improved the prediction of SGA provided by maternal history alone.

In pregnancies resulting in spontaneous preterm delivery the maternal serum concentration of TNF-R1 at 11–13 weeks was not significantly different from normal. Previous studies have implicated TNF-α and other proinflammatory cytokines in preterm delivery because they demonstrated increased levels in amniotic fluid from women presenting in preterm labor irrespective of the presence or absence of infection[33–36]. In addition, genetic studies have reported that women with certain *TNF* gene polymorphisms are at increased risk for preterm delivery[37,38]. However, studies examining maternal serum levels of cytokines did not find an association with preterm delivery either in samples taken before or during preterm labor[39,40].

In pregnancies that subsequently develop pre-eclampsia the maternal serum TNF-R1 concentration at 11–13 weeks of gestation is increased. Although this finding provides further support for an inflammatory process in the pathogenesis of pre-eclampsia, measurement of TNF-R1 is not useful in the early prediction of the disease.

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