ORIGINAL ARTICLE

Maternal serum cytokines at 30–33 weeks in the prediction of preeclampsia

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ABSTRACT

Objective The aim of this case–control study at 30–33 weeks, a few days or weeks before the clinical onset of preeclampsia (PE), was to assess whether serum concentrations of cytokines differ between patients who are destined to develop PE and those with uncomplicated pregnancies.

Methods A panel of cytokines was measured using Luminex technology at 30–33 weeks' gestation in 39 cases that developed PE at or after 34 weeks and 117 unaffected controls.

Results The serum concentrations of most analysed cytokines were no different in women who developed PE than in controls. The proportions of women with detectable concentrations of MIP-1α and IL-8 were significantly lower in those with PE than in the controls (MIP-1α: 14/39 vs 76/117, $P = 0.003$; IL-8:13/39 vs 83/117, $P < 0.0001$). The median maternal serum concentration of IL-1β was significantly lower in the PE cases than in the controls (0.38 pg/mL, range 0.01–0.92, vs 0.60 pg/mL, range 0.02–3.54, $P = 0.005$).

Conclusion Our findings do not lend support to the hypothesis that systemic inflammation precedes the onset of PE or that cytokines are good markers for such inflammation and certainly the panel of cytokines we examined does not provide useful prediction of subsequent development of PE. © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

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INTRODUCTION

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality.[1–3] The underlying mechanism for the development of PE is thought to be impaired trophoblastic invasion and remodelling of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control.[4–7] Impaired placental perfusion leads to placental ischaemia and damage with release of inflammatory factors that cause platelet activation and endothelial dysfunction and consequent development of the clinical symptoms of the disease.[8–10]

Several cytokines have been suggested to be the placental factors capable of damaging endothelial cells and contributing to many of the pathophysiological changes associated with PE.[11–13] Supportive evidence is provided by the results of many studies in women with established PE, which reported that the circulating levels of specific cytokines are increased (Table 1, S1-S44). However, the finding that established PE is accompanied by systemic inflammation does not necessarily support the role of cytokines in the development of the disease.

The aim of this case–control study at 30–33 weeks, a few days or weeks before the clinical onset of PE, was to assess whether serum concentrations of cytokines differ between patients who are destined to develop PE and those with uncomplicated pregnancies.

METHODS

This was a case–control study drawn from a prospective observational study for adverse pregnancy outcomes in women attending for their routine third trimester hospital visit in pregnancy at King's College Hospital London between May 2011 and March 2012. The third trimester visit, at 30^{+0}–33^{+6} weeks' gestation, included ultrasound examination for assessment of foetal growth and well-being. Maternal blood was collected for research, and the serum was stored at −80 °C for subsequent biochemical analysis. Written

Table 1 **Studies assessing cytokine levels in overt preeclampsia. Conflicting results may be partly from the different assays used, different definitions of preeclampsia as well as different gestational ages at blood draw**

		During preeclampsia		
Cytokine	Main functions	Not different	Higher	Lower
TNF-α	Pro-inflammatory	S1, S2, S3, S4, S5	S6, S7, S8, S9, S10, S11, S12	
IL-1β	Pro-inflammatory	S1, S2, S3, S4, S6, S12, S18, S34	S15	
IL-6	Pro-inflammatory	S1, S2, S13	S3, S5, S6, S7, S9, S10, S11, S12, S14, S15, S16, S17, S18, S19	
IL-18	Pro-inflammatory	S42	S6, S23, S43, S44	S14
IP-10	Pro-inflammatory Angiogenetic chemoattraction		S1, S6, S41	
MIP-1α	Pro-inflammatory	S3		
MIP-1β	Pro-inflammatory	S2, S3		
IL-1ra	Anti-inflammatory	S34	S6	
IL-10	Anti-inflammatory	S1, S2, S3, S12, S23	S6, S10	S7, S13, S21
IL-8	Angiogenetic pro-inflammatory	S1, S2	S3, S6, S7, S9, S20, S35	
VEGF	Angiogenetic		S27, S28	S29, S30, S31, S32, S33
ICAM	Cell adhesion Endothelial dysfunction Pro-inflammatory	S36, S37	S6, S38, S39, S40	
VCAM	Cell adhesion Endothelial dysfunction Pro-inflammatory	S37	S6, S36, S38, S39, S40	
IL-2	Immunmodulatory Pro-inflammatory	S1, S2, S3, S13	S6, S8, S11	
IL-4	Immunmodulatory Pro-inflammatory	S2, S3, S20, S21	S6, S23	S1
IL-12p70	Immunmodulatory Pro-inflammatory anti-angiogenetic	S2, S20	S6, S22, S23, S24	
IL-15	Immunmodulatory Pro-inflammatory	S3	S23, S24, S25, S26	
IFN-γ	Immunmodulatory Pro-inflammatory	S1, S2, S3, S20, S21, S22	S5, S6, S8, S23	
Basic FGF	Angiogenetic			
MCP-1	Immunmodulatory Pro-inflammatory Atherosclerotic	S2, S3	S6, S35	

TNF-α, tumour necrosis factor-alpha; IL-1β,interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; IP-10, interferon gamma-induced protein 10; MIP-1α, macrophage inflammatory protein-1 alpha; MIP-1β, macrophage inflammatory protein-1 beta; IL-1ra, interleukin 1 receptor antagonist; IL-10, interleukin-10; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; ICAM, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule-1; IL-2, interleukin-2; IL-14, interleukin-4; IL-12p70,interleukin-12p70; IL-15, interleukin-15, IFN-γ, interferon gamma; basic FGF, basic fibroblast growth factor; MCP-1, monocyte chemotactic protein-1.

informed consent was obtained from the women agreeing to participate in the study that was approved by the Ethics Committee of each participating hospital.

The base cohort study population, wherein the present case–control study was nested, constituted 5099 singleton pregnancies. We excluded 244 cases because they had missing outcome data ($N=156$), they had PE at the time of screening or before 34 weeks ($N=25$), the pregnancy resulted in delivery before 34 weeks' gestation ($N=37$) or the birth of babies with major defects ($N=26$). In the remaining 4855 cases, there were 145 (3.0%) cases that developed PE. There was available stored maternal blood from 39 cases that developed PE. These women were demographically and obstetrically no different from the remaining 106 cases for whom serum was not available. Each case of PE was matched with three 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.

Patient characteristics including maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after

Table 2 Representative assay working ranges,[a] assay sensitivity, and precision.[b] The lower limit of quantitation (LLOQ), upper limit of quantitation (ULOQ), limit of detection (LOD), and intra-assay/inter-assay coefficient of variation (% CV) are mean data determined from five assays in serum-based matrix

	Assay working Ranges, pg/ml		Assay sensitivity, pg/ml	Assay precision	
Targets	LLOQ	ULOQ	LOD	Intra-assay %CV	Inter-assay %CV
TNF-α	5.8	95 484	6.0	8	6
IL-1β	3.2	3261	0.6	6	8
IL-6	2.3	18 880	2.6	7	11
IL-18	1.8	28 677	0.2	4	5
IP-10	18.8	26 867	6.1	11	9
MIP-1α	1.4	836	1.6	7	8
MIP-1β	2.0	1726	2.4	8	8
IL-1ra	81.1	70 487	5.5	9	9
IL-10	2.2	8840	0.3	5	6
Il-8	1.9	26 403	1.0	9	4
VEGF	5.5	56 237	3.1	9	7
ICAM	13	26 368	2.4	4.3	3.8
VCAM	38	21 430	0.6	6.7	5.5
IL-2	2.1	17 772	1.6	7	9
IL-4	2.2	3467	0.7	9	8
IL-12p70	3.3	13 099	3.5	6	6
IL-15	2.1	2799	2.4	5	6
IFN-γ	92.6	52 719	6.4	15	9
Basic FGF	27.2	7581	1.9	8	8
MCP-1	2.1	1820	1.1	9	7

LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation; LOD, limit of detection; %CV, intra-assay/inter-assay coefficient of variation; TNF-α, tumour necrosis factor-alpha; IL-1β,interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; IP-10, interferon gamma-induced protein 10; MIP-1α, macrophage inflammatory protein-1 alpha; MIP-1β, macrophage inflammatory protein-1 beta; IL-1ra, interleukin 1 receptor antagonist; IL-10, interleukin-10; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; ICAM, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule-1; IL-2, interleukin-2; IL-14, interleukin-4; IL-12p70,interleukin-12p70; IL-15, interleukin-15, IFN-γ, interferon gamma; basic FGF, basic fibroblast growth factor; MCP-1, monocyte chemotactic protein-1.

[a]Assay range is LLOQ and ULOQ, calculated from five independent assays.

[b]Data were generated using vacuum manifold. %CV is expected to be comparable or lower with magnetic bead washer.

24 weeks), previous pregnancy with PE (yes or no) and maternal weight and height were recorded.

Preeclampsia was defined according to the criteria established by the International Society for the Study of Hypertension in Pregnancy[14], systolic blood pressure of 140 mmHg or more and/or the diastolic blood pressure 90 mmHg or more developing after 20 weeks of gestation together with significant proteinuria in a previously normotensive woman. 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 earlier) 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).

A panel of cytokines, which have all been previously described to be altered in PE and have their main function in immune interactions, inflammation and angiogenesis, was chosen. Cytokines have pleiotropic functions, according to their most important function, tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), interferon gamma-induced protein 10 (IP-10), macrophage inflammatory protein-1 alpha (MIP-1α) and macrophage inflammatory protein-1 beta (MIP-1β) that are all pro-inflammatory cytokines; interleukin 1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10) have anti-inflammatory function; interleukin-8 (IL-8) and free vascular endothelial growth factor (VEGF) are angiogenetic cytokines, whereas intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are responsible for cell adhesion and endothelial dysfunction. Interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-12p70 (IL-12p70), interleukin-15 (IL-15), interferon gamma (IFN-γ), basic fibroblast growth factor (basic FGF) and monocyte chemotactic protein-1 (MCP-1) are involved in immune cell interactions. The representative assay working ranges, assay sensitivity and precision are presented in Table 2.

Serum samples were collected from the antecubital vein and stored at −80 °C after centrifugation until analysis. Cytokines were measured by Luminex technology using Biorad Bio-plex kits (Bio-Rad Laboratories, Hercules, CA, USA). Pre-mixed standards were reconstituted and serially diluted to generate a standard curve. The assays were performed in 96 well filtration plates as supplied with the kit. Pre-mixed beads coated with the target capture antibodies were then added (5000/well/cytokine) and washed twice. Pre-mixed standards and neat serum were then added, the plate shaken and incubated at room temperature for 30 min with continuous low speed shaking. After a further washing step, pre-mixed detection antibodies were added and incubated with shaking for 10 min. The plate was then washed three times and the beads re-suspended in wash buffer. The plates were read using Biorad Bio-plex suspension array system and analysed using Bio-plex Manager software. ELISA technology is considered the gold standard for measurement of cytokines, but it is rarely used because of the need for big sample volumes and high costs. Multiplex assays overcome these problems and have been shown to produce comparable results with those of ELISA.[15–17]

Comparisons of maternal characteristics between outcome groups were by Chi-square or Fisher exact test for categorical variables and by Mann Whitney-*U* test for continuous variables. The proportions of detectable cytokines in cases and controls are presented in numbers and percentages and were compared by Chi-square or Fisher exact test. The median (range) serum concentration of each cytokine between the cases and controls were compared by Mann Whitney-*U* test.

The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp, Armonk, NY, USA) was used for all data analyses.

RESULTS

The maternal characteristics of the case–control study population are given in Table 3. In the PE group, compared with the control group, there was a higher prevalence of women with personal history of previous PE and chronic hypertension.

The maternal serum concentrations of TNF-α, IL-2, IL-6, IFN-γ, IL-4, IL-15, basic FGF and VEGF were detectable in less than 10% of the samples (Table 4). The proportion of women with detectable concentrations of each of these markers was not significantly different between those with PE and the controls. The maternal serum concentrations of IL-1β, MIP-1α, IL-1ra, IL-10, IL-8, IL-12p70, MCP-1, ICAM-1 and VCAM-1 were detectable in more than 10% but certainly not all of the samples (Table 3). The proportion of women with detectable concentrations of MIP-1α and IL-8 were significantly lower in those with PE than in the controls (MIP-1α: 14/39 vs. 76/117, $P = 0.003$; IL-8: 13/39 vs 83/117, $P < 0.0001$). The median maternal serum concentration of IL-1β was significantly lower in the PE cases than in the controls (0.38 pg/mL, range

Table 3 **Maternal characteristics in outcome groups**

Characteristic	Control ($N = 117$)	Preeclampsia ($N = 39$)	*P*-value
Maternal age in years, median (IQR)	30.9 (27.4–34.1)	30.2 (27.5–34.3)	0.993
Maternal weight in kg, median (IQR)	75.8 (68.8–84.9)	77.2 (68.0–90.2)	0.271
Maternal height in cm, median (IQR)	166 (162–169)	164 (160–167)	0.064
Body mass index in kg/m^2, median (IQR)	28.1 (24.9–30.8)	29.6 (26.4–33.3)	0.052
Gestation at sampling in weeks, median (IQR)	32.0 (32.0–32.3)	32.0 (32.0–32.3)	0.321
Racial origin			
Caucasian, *n* (%)	64 (54.7)	17 (43.6)	0.269
Afro-Caribbean, *n* (%)	45 (38.5)	18 (46.2)	0.453
South Asian, *n* (%)	5 (4.3)	0 (0.0)	0.332
East Asian, *n* (%)	2 (1.7)	2 (5.1)	0.260
Mixed, *n* (%)	1 (0.9)	2 (5.1)	0.154
Parity			
Nulliparous, *n* (%)	74 (63.2)	22 (56.4)	0.454
Parous with no previous preeclampsia, *n* (%)	43 (36.8)	14 (35.9)	>0.999
Parous with previous preeclampsia, *n* (%)	0 (0)	3 (7.7)	0.015*
Cigarette smoker, *n* (%)	6 (5.1)	3 (7.7)	0.692
Family history of preeclampsia, *n* (%)	5 (4.3)	3 (7.7)	0.413
Conception			
Spontaneous, *n* (%)	115 (98.3)	37 (94.9)	0.260
Assisted, *n* (%)	2 (1.7)	2 (5.1)	0.260
History of chronic hypertension, *n* (%)	0 (0)	3 (7.7)	0.015*
Gestational age at delivery, median (IQR)	40.2 (39.4–41.0)	38.9 (37.5–40.3)	<0.0001*
Birth weight in g, median (IQR)	3,420 (3,140–3,704)	3,026 (2,482–3,496)	<0.0001*
Small for gestation (<10th centile), *n* (%)	6 (5.1)	13 (33.3)	<0.0001*

Comparisons between each outcome group with controls: Chi square test and Fisher exact test for categorical variables and Mann Whitney-*U* test. IQR, interquartile range.
*$P < 0.05$.

0.01–0.92, vs 0.60 pg/mL, range 0.02–3.54, $P=0.005$), but there was no significant association between IL-1β levels and the gestational age at delivery ($r=-0.161$, $P=0.511$). The serum concentrations of IP-10, MIP-1β and IL-18 were detectable in all of the samples. The median maternal serum concentrations of these markers were not significantly different between the cases and controls.

The maternal serum concentrations of the inflammation related markers IL-1β, MIP-1α, IL-1ra, IL-10, IP-10 and MIP-1β are presented in Figure 1. The concentrations of the neutrophil-associated IL-8 and the Th1-associated IL-12p70 and the markers of endothelial dysfunction ICAM-1 and VCAM-1 are presented in Figure 2.

DISCUSSION

In this study, we examined the maternal serum concentration of a panel of cytokines a few days or weeks before the clinical development of PE and demonstrated that for most cytokines, the serum levels were not significantly different from pregnancies with normal outcome. These findings suggest that

Table 4 Detectable cases and median (range) in pg/mL of cytokines in preeclampsia cases and controls. Values beyond LOD are extrapolated

Cytokine	Preeclampsia ($N=39$)	Control ($N=117$)	*P*-value
Detectable in <10% of samples			
	N (%)	*N* (%)	
TNF-α	2 (5.1%)	9 (7.7%)	0.732
IL-2	0 (0%)	2 (1.8%)	>0.999
IL-6	3 (7.7%)	11 (9.4%)	>0.999
IFN-γ	1 (2.6%)	0 (0%)	0.250
IL-4	1 (2.6%)	0 (0%)	0.250
IL-15	0 (0%)	0 (0%)	>0.999
Basic FGF	2 (5.1%)	7 (6.0%)	>0.999
VEGF	1 (2.6%)	8 (6.8%)	0.452
Detectable in >10% of samples			
	N (%) Median pg/mL (range)	N (%) Median pg/mL (range)	
IL-1β	20 (51.3%) 0.38 (0.01–0.92)	81 (69.2%) 0.60 (0.02–3.54)	0.053 0.005*
MIP-1α	14 (35.9%) 1.32 (0.48–13.1)	76 (65.0%) 1.19 (0.26–306.73)	0.003* 0.668
IL-1ra	9 (23.1%) 39.02 (2.23–505.28)	25 (21.4%) 37.69 (1.79–1,090.46)	0.825 0.653
IL-10	9 (23.1%) 1.30 (0.21–3,498.65)	48 (41.0%) 0.63 (0.01–35.90)	0.055 0.279
IL-8	13 (33.3%) 3.27 (0.61–6.08)	83 (70.9%) 3.50 (0.33–60.24)	<0.0001* 0.641
IL-12p70	10 (25.6%) 1.93 (0.67–247.64)	39 (33.3%) 1.48 (0.06–86.04)	0.430 0.243
MCP-1	24 (61.5%) 6.42 (0.58–42.78)	67 (57.3%) 10.60 (0.12–54.47)	0.710 0.918
ICAM-1	39 (100.0%) 179.44×10^3 ($93.02–251.77 \times 10^3$)	114 (97.4%) 169.83×10^3 ($65.96–415.98 \times 10^3$)	0.574 0.161
VCAM-1	36 (92.3%) 241.20×10^3 ($136.01–315.88 \times 10^3$)	111 (94.9%) 227.10×10^3 ($130.00–418.64 \times 10^3$)	0.692 0.276
Detectable in all samples			
	Median pg/mL (range)	Median pg/mL (range)	
IP-10	1028.62 (312.56–2,963.41)	878.25 (359.26–11,969.87)	0.167
MIP-1β	92.16 (35.66–188.21)	89.41 (26.03–316.04)	0.405
IL-18	72.45 (25.62–415.56)	71.94 (17.18–224.85)	0.716

TNF-α, tumour necrosis factor-alpha; IL-1β,interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; IP-10, interferon gamma-induced protein 10; MIP-1α, macrophage inflammatory protein-1 alpha; MIP-1β, macrophage inflammatory protein-1 beta; IL-1ra, interleukin 1 receptor antagonist; IL-10, interleukin-10; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; ICAM, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule-1; IL-2, interleukin-2; IL-14, interleukin-4; IL-12p70,interleukin-12p70; IL-15, interleukin-15, IFN-γ, interferon gamma; basic FGF, basic fibroblast growth factor; MCP-1, monocyte chemotactic protein-1.
*$P<0.05$.

neither systemic inflammation nor immune dysfunction precedes the onset of PE. However, it is possible that the cytokines we examined are not good markers of such pathological changes.

Cytokines are typically involved in the regulation of recruitment, activation, proliferation and cell-to-cell communication of the immune system.[18] They essentially affect every cell type in the body and have pleiotropic regulatory effects on haematopoietic, endocrine, nervous and immune systems.[19–21] Pregnancy-specific immunomodulation is thought to be essential for successful initiation, maintenance and completion of pregnancy.[22,23] The placenta produces a wide variety of pro-inflammatory and anti-inflammatory cytokines and cytokine-like angiogenic growth factors,[24] and in normal pregnancy, there is a systemic inflammatory response that is thought to be exaggerated in PE.[25] Supportive evidence for this is provided by the results of several, but not all, previous studies which demonstrated that in pregnancies with established PE, the serum levels of cytokines involved in inflammation and endothelial dysfunction, including TNF-α, IL-6, IL-8, IL-12p70, IL-15, IL-18, IP-10, ICAM and VCAM are increased (Table 1). The conflicting results from some of the previous studies may be the consequence of differences in the assays used for the measurements, the definitions of PE as well as gestational ages at blood draw.

Our findings that at 30–33 weeks' gestation the serum levels of cytokines that are not altered in women that subsequently develop PE suggest that the inflammatory response observed in association with PE (Table 1) may not precede the clinical onset of the disease. Our results are compatible with those of one previous longitudinal study examining nine pro-inflammatory cytokines (IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, INF-γ, TNF-α) in 32 cases that developed PE and 67 controls reporting no consistent difference between the groups at <25 weeks'

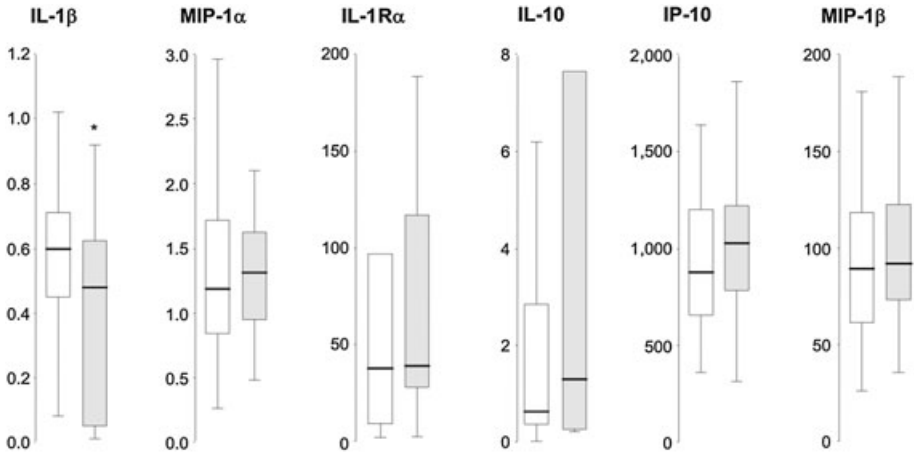

Figure 1 Maternal serum concentrations (pg/mL) at 30–33 weeks' gestation of the inflammation related markers IL-1β, MIP-1α, IL-1ra, IL-10, IP-10 and MIP-1β in pregnancies that developed preeclampsia (grey boxes) and controls

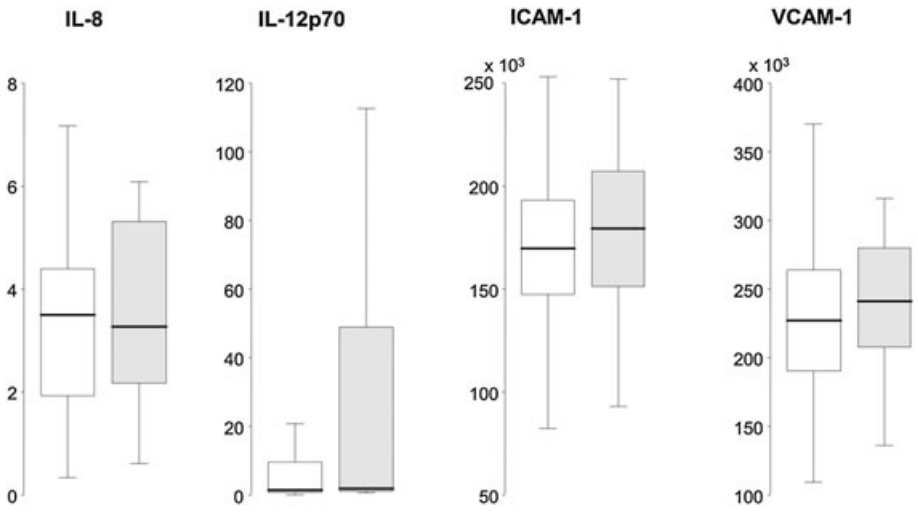

Figure 2 Maternal serum concentrations (pg/mL) at 30–33 weeks' gestation of the neutrophil associated IL-8 and the Th1 associated IL-12p70 and the markers of endothelial dysfunction ICAM-1 and VCAM-1 in pregnancies that developed preeclampsia (grey boxes) and controls

gestation, at 25–29 weeks, 30–35 weeks or >36 weeks.[26] A recent study has reported that in pregnancies developing PE, the maternal serum concentration of TNF receptor-1, a pro-inflammatory cytokine, is significantly increased both at 11–13 and at 30–33 weeks' gestation.[27] Such a finding are suggestive of an inflammatory process that precedes the clinical onset of the disease. However, increased serum levels of C-reactive protein, a non-specific marker of inflammation, as well as other acute phase proteins are observed during PE but not consistently so before the development of the disease.[28–31]

In our study, the only significant differences between the PE group and controls was the lower level in serum IL-1β and lower frequency of detectable levels for IL-8 and MIP-1α. These three cytokines are considered to be pro-inflammatory and would therefore be expected to be increased rather than decreased in the PE group. During normal pregnancy, trophoblast debris are shed from the placenta into the maternal circulation where they are rapidly cleared through phagocytosis by macrophages.[32] This process in turn leads to a change in cell-surface markers in macrophages and in their secretion of cytokines, including reduced production of IL-1β and IL-8.[32] It is possible that the observed down regulation of IL-1β, IL-8 and MIP-1α in PE is the consequence of placental oxidative stress and the related increased shedding of trophoblast debris.[33]

An imbalance of angiogenic and anti-angiogenic factors has been proposed to contribute to the development of PE. There is extensive evidence demonstrating that placental growth factor, an angiogenic factor, is reduced in women who are to develop PE, whereas soluble fms-like tyrosine kinase-1 (s-Flt), an anti-angiogenic factor, is found to be increased. [34–36] The reduction in PlGF and the increase in s-Flt are most pronounced in the third trimester, a few days or weeks prior to the development of late onset PE. Such hypothesis of angiogenic/anti-angiogenic imbalance is further supported by the finding of our study that IL-8, an angiogenetic cytokine, is significantly reduced at 30–33 weeks in women developing PE. However, the levels of the other cytokines with angiogenic properties (VEGF, basic FGF, IP-10 and IL 12p70) are not significantly altered.

A limitation of the study is the higher prevalence of women with chronic hypertension in the PE group as gene expression and activation might be different in this group of women.[37] However, we did not demonstrate the anticipated increase in the levels of inflammatory cytokines in the PE group.

CONCLUSION

In conclusion, our findings do not lend support to the hypothesis that systemic inflammation precedes the onset of PE or that cytokines are good markers for such inflammation and certainly, the panel of cytokines we examined does not provide useful prediction of subsequent development of PE.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- In pregnant women with preeclampsia, the circulating maternal serum levels of many cytokines are increased. Little is known about their levels prior to the onset of clinical signs of preeclampsia.

WHAT DOES THIS STUDY ADD?

- Most cytokines are not different in women who will develop preeclampsia compared with healthy controls. This questions the role of significant immune dysfunction and systemic inflammation prior to the onset of preeclampsia.

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