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First trimester inflammatory mediators in women with chronic hypertension

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Abstract

Introduction: Chronic hypertension complicates 1%-2% of pregnancies and is one of the most significant risk factors for the development of preeclampsia. Inflammatory mediators, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), vascular cell adhesion molecule (VCAM) and endothelin have been implicated in the endothelial dysfunction that is pathognomonic of preeclampsia and may serve as useful first trimester biomarkers for the prediction of preeclampsia. The objectives of this study are: first, to investigate differences in serum levels of IL-6, TNF-α, VCAM and endothelin at 11^{+0} to 13^{+6} weeks' gestation in women with chronic hypertension who developed superimposed preeclampsia with those who did not and normotensive controls and, second, to evaluate the performance of these biomarkers in the prediction of preeclampsia.

Material and methods: The study population was comprised of 650 women with chronic hypertension, including 202 who developed superimposed preeclampsia and 448 who did not, and 142 normotensive controls matched to the chronic hypertension group for storage time and racial origin. Serum concentrations of IL-6, TNF-α, VCAM and endothelin were measured and the values were converted into multiples of the expected median using multivariate regression analysis in the control group. The multiples of the median values of the biomarkers between the two groups of women with chronic hypertension and the controls were compared, and the receiver operating characteristic curve (ROC) was used to assess the performance of these variables for the prediction of preeclampsia.

Results: In women with chronic hypertension, compared with the normotensive controls, there was a significantly higher first trimester median concentration of endothelin but not of VCAM, IL-6 or TNF-α. Within the cohort of women with chronic hypertension, those who developed superimposed preeclampsia, compared with those who did not, had higher first trimester serum concentration of VCAM but not of endothelin, IL-6 or TNF-α. However, serum VCAM provided a poor prediction of superimposed preeclampsia (area under the ROC curve 0.537, 95% CI 0.487-0.587).

Abbreviations: CH, chronic hypertension; CI, , confidence interval; IL-6, interleukin-6; MoM, multiples of the median; OR, , odds ratio; PE, preeclampsia; ROC, receiver operating characteristic; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule.

Conclusions: Women with chronic hypertension have increased serum endothelin in the first trimester of pregnancy and those who develop superimposed preeclampsia have higher levels of VCAM. None of the inflammatory mediators performed well in the first trimester in the prediction of preeclampsia.

KEYWORDS

chronic hypertension, endothelin, inflammatory mediators, interleukin-6, preeclampsia, tumor necrosis factor-α, vascular cell adhesion molecule

1 | INTRODUCTION

One of the greatest risk factors for preeclampsia (PE) is a medical history of chronic hypertension (CH), which complicates 1%-2% of pregnancies.[1] After adjustment for maternal characteristics, the risk of PE is 5-6 times higher in women with CH than in those without CH.[1] Effective first trimester screening for PE using a combination of maternal biomarkers and characteristics could help to identify the high-risk group of women with CH who may benefit more from prevention strategies such as stricter control of blood pressure.

It is generally accepted that in normal pregnancy, pro-inflammatory mediators and cell adhesion molecules play a vital role in the establishment and maintenance of pregnancy.[2,3] For example, decidual expression of tumor necrosis factor (TNF-α) and interleukin (IL-6) is thought to modulate trophoblast growth and differentiation, and invasion of spiral arteries and to be involved in parturition.[2] Similarly, the production of cell adhesion molecules, such as vascular cell adhesion molecule (VCAM), is upregulated by pro-inflammatory cytokines and helps to mediate the interaction between the invading trophoblasts and endometrial cells.[3]

In PE, in particular preterm PE, it has been proposed that this physiological inflammatory response is exaggerated and triggered by impaired placentation.[4] This then leads to the systemic endothelial dysfunction that underlies many of the signs and symptoms of the disease.[4] Several studies have reported that the maternal serum concentration of many pro-inflammatory mediators, such as endothelin,[5] IL-6,[6] TNF-α[6] and VCAM,[6] is increased in women with PE compared with normotensive controls at the point of diagnosis of the disease. Furthermore, infusion of TNF-α into pregnant rats induces a PE-like syndrome mediated in part by endothelin.[7] Consequently, these inflammatory markers of endothelial dysfunction may serve as first trimester predictors of PE. However, in women with CH, endothelial dysfunction already preexists[8] with varying severity and, therefore, prior to their inclusion into screening algorithms, evaluation in this high-risk subgroup is needed.

The objectives of this study are, first, to investigate differences between serum levels of IL-6, TNF-α, VCAM and endothelin at 11^{+0} to 13^{+6} weeks' gestation in women with CH who developed superimposed PE to those who did not and normotensive controls and, second, to evaluate the performance of these biomarkers in the prediction of PE.

Key message

In women with chronic hypertension the performance of first trimester serum inflammatory markers in the prediction of superimposed preeclampsia is poor.

2 | MATERIAL AND METHODS

2.1 | Study population

This was a case-control study involving the analysis of serum IL-6, TNF-α, VCAM and endothelin in stored samples (−80°C) obtained at 11^{+0}-13^{+6} weeks' gestation from 650 singleton pregnancies complicated by CH and 142 normotensive controls attending for pregnancy care at King's College Hospital, London, UK, between January 2011 and September 2018. Women were classified as CH if they had pre-pregnancy hypertension or have blood pressure ≥ 140/90 mmHg on two consecutive clinical visits prior to 20 weeks' gestation in the absence of renal or liver disease.[9] Gestational age was determined from measurement of fetal crown-rump length. As per guidelines, all women with CH were commenced on low-dose aspirin in the first trimester.[10]

2.2 | Assay analysis

2.2.1 | TNF-α and IL-6

Serum concentrations of TNF-α and IL-6 were determined using the Meso Scale Proinflammatory 2 Plex (Mesoscale Discovery, Rockville, MD, USA). The detection limits were 0.04 and 0.06 ng/L for TNF-α and IL-6, respectively, with a measurement range from 0.10 to 1.75 ng/L and 0.16 to 27.2 ng/L for TNF-α and IL-6, respectively. The intra-assay coefficients of variation for the low and high concentrations were 10.1% and 6.1% for TNF-α, and 4.5% and 3.6% for IL-6. The inter-assay coefficients of variation for the low and high concentrations were 6.2% and 7.2% for TNF-α and 7.3% and 5.2% for IL-6.

2.2.2 | Endothelin

Serum concentrations of endothelin were determined using the Quantikine Endothelin-1 ELISA kit (Biotechne, R&D Systems, Abingdon, UK). The detection limit was 0.09 ng/L with a measurement range of 0.45-2.00 ng/L. The intra-assay coefficients of variation for the low and high concentrations were 4.0% and 1.9%. The inter-assay coefficients of variation for the low and high concentrations were 7.6% and 5.3%.

2.3 | VCAM

Serum concentrations of VCAM were determined using the Quantikine VCAM ELISA kit (Biotechne). The detection limit was 0.60 μg/L with a measurement range 349-991 μg/L. The intra-assay coefficients of variation for the low and high concentrations were 2.3% and 3.6%. The inter-assay coefficients of variation for the low and high concentrations were 7.8% and 5.5%.

2.4 | Inclusion and exclusion criteria

The inclusion criteria for this study were singleton pregnancies resulting in the live birth or stillbirth of phenotypically normal babies at ≥24 weeks' gestation. We excluded pregnancies with fetal aneuploidies or major defects diagnosed in the antenatal or neonatal period and pregnancies ending in miscarriage at <24 weeks' gestation.

For every five cases with CH we selected approximately one control from normotensive pregnancies that resulted in the live birth of non-malformed neonates and were matched to the cases for storage time of maternal serum and racial origin, because the incidence of CH is three times higher in black than white women.[1] The power calculation was based on a previous study on angiogenic markers in women with CH.[11]

2.5 | Definitions of adverse pregnancy outcomes

Data on pregnancy outcomes were collected from the hospital maternity records. Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy as the presence of hypertension along with at least one of the following: renal involvement (proteinuria ≥300 mg/24 hour and/or serum creatinine ≥90 μmol/L or 1 mg/dL), liver impairment (serum transaminases >70 IU/L), neurological complications (eg eclampsia), thrombocytopenia (platelet count <150 000/μL), uteroplacental insufficiency with fetal growth restriction.[9] Preeclampsia was subdivided into preterm with onset at <37 weeks' gestation and term with onset at ≥37 weeks' gestation. Severe hypertension was defined by the presence of systolic blood pressure >160 mmHg and/ or diastolic blood pressure >110 mmHg. Small for gestational age was defined as birthweight <10th percentile without adjustment for maternal characteristics.[12]

2.6 | Statistical analyses

Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. The distribution of IL-6, TNF-α, VCAM and endothelin were logarithmically transformed to approximate Gaussian distribution. Comparison of maternal characteristics between the two groups of women with CH and the controls was by the Chi-square test for categorical variables or by the analysis of variance (ANOVA) and Kruskal-Wallis test with Bonferroni correction for post-hoc analysis for normally and non-normally distributed continuous variables, respectively. Numerical data were expressed as median and interquartile range. The measured log IL-6, log VCAM and log endothelin were converted to multiples of the median (MoM) of the control group, after adjustment for maternal characteristics. The performances of MoM log IL-6, MoM log VCAM, MoM log endothelin and log TNF-α for the prediction of PE were assessed by univariate logistic regression and the receiver operating characteristic (ROC) curve.

Due to the matched cased-control design we performed a sensitivity analysis in the form of a matched-samples analysis (Mantel-Haenszel test or conditional logistic regression for categorical variables, paired-samples ANOVA or Friedman's ANOVA for continuous variables) and presented as supplementary material.

Statistical analysis was performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA).

2.7 | Ethical approval

Written informed consent was obtained from women who agreed to participate in the study on early prediction of pregnancy complications, approved on 17 February 2017 by the National Health Service Health Research Authority, Dulwich Research Ethics Committee (REC reference 02-03-033).

3 | RESULTS

3.1 | Population characteristics

During the study period, 448 pregnancies with CH that did not develop PE and 202 with CH that did, met the inclusion criteria. The control group consisted of 142 normotensive women. The maternal characteristics of the two groups with CH and the controls are compared in Table 1. In pregnancies with CH, compared with controls, median maternal age and systolic and diastolic blood pressure at 11-13 weeks' gestation were higher. In pregnancies with CH that developed PE, compared with those who did not, there were higher proportions of previous PE, family history of PE and use of antihypertensive medications at 11-13 weeks' gestation. (Table 1).

In pregnancies with CH, compared with controls, there was a higher proportion of small-for-gestational age neonates with a lower median gestational age at delivery and birthweight percentile (Table 1). In pregnancies with CH that developed PE, compared with those who

TABLE 1 Comparison of maternal and pregnancy characteristics between normotensive controls, women with chronic hypertension who did not develop superimposed preeclampsia and those who did

Variable	Controls (N = 142)	Chronic hypertension		Overall *P* value
		No preeclampsia (n = 448)	Preeclampsia (n = 202)	
Characteristics at 11-13 weeks				
Age (years), median (IQR)	31.5 (28.2-34.5)[a,b]	34.0 (31.0-38.0)	34.0 (31.0-38.0)	<.0001
Weight (kg), median (IQR)	81.9 (71.7-90.0)	84.5 (71.6-97.0)	83.0 (69.9-97.0)	NS
Height (meters), median (IQR)	165.0 (160.0-169.6)	165.0 (161.0-170.0)	165.0 (160.0-168.3)	NS
Body mass index (kg/m^2), median (IQR)	30.1 (26.6-33.5)	31.0 (26.0-36.0)	31.0 (26.0-35.6)	NS
Gestational age of nuchal scan, median (IQR)	12.7 (12.3-13.1)	12.7 (12.3-13.1)	12.6 (12.3-13.0)	NS
Racial origin				
Black, n (%)	87 (61.3)	257 (57.4)	132 (65.3)	NS
White, n (%)	52 (36.6)	150 (33.5)	59 (29.2)	NS
Other, n (%)	3 (2.2)[a,b]	41 (9.2)[b]	11 (5.4)	.011
Parous, n (%)	102 (71.8)	311 (69.4)	135 (66.8)	NS
Previous preeclampsia, n (%)	5.0 (3.5)[a,b]	163 (36.4)	92 (45.5)[c]	<.0001
Family history of preeclampsia, n (%)	7.0 (4.9)[a,b]	51 (11.4)	35 (17.3)[c]	.002
Systolic BP (mmHg), median (IQR)	118.1 (112.9-125.0)[a,b]	130.0 (120.0-140.0)	130.0 (120.0-140.0)	<.0001
Diastolic BP in (mmHg), median (IQR)	73.0 (66.0-77.1)[a,b]	80.0 (74.0-88.0)	80.0 (75.0-90.0)	<.0001
Antihypertensive medications, n (%)		228 (50.9)	142 (70.2)[c]	<.0001
Pregnancy outcome				
Antihypertensive medications at delivery, n (%)		227 (50.7)	181 (89.6)[c]	<.0001
Severe hypertension, n (%)		68 (15.2)	86 (42.6)[c]	<.0001
Preterm preeclampsia, n (%)		-	119 (58.9)	–
Gestation at delivery, median (IQR)	40.2 (39.4-40.9)[a,b]	39.1 (38.4-40.1)	37.7 (35.6-38.9)[c]	<.0001
Birthweight percentile, median (IQR)	45.6 (30.2-69.0)[b]	42.3 (21.7-69.7)	13.9 (1.2-52.7) [c]	<.0001
Birthweight <10th centile, n (%)	2 (1.4)[a,b]	52 (11.6)	92 (45.5)[c]	<.0001

Abbreviations: BP, blood pressure; IQR, interquartile range.

[a]Statistically significant difference between the controls and the group with chronic hypertension who did not develop preeclampsia.

[b]Statistically significant difference between the controls and the group with chronic hypertension who developed preeclampsia.

[c]Statistically significant difference in the chronic hypertension group between those who developed preeclampsia and those who did not.

did not, there were higher proportions of treatment with antihypertensive drugs at the time of delivery, development of severe hypertension and delivery of small-for-gestational-age neonates and lower median gestational age at delivery and birthweight percentile. (Table 1).

3.2 | Serum IL-6, TNF-α, VCAM and endothelin

3.2.1 | Creation of multiples of the median using data from normotensive controls

In the multiple regression model for log VCAM, significant independent contributions were provided by black racial origin ($P \leq .01$, $R^2 = 0.067$): Log VCAM expected = 2.754330 − 0.051222 × black racial origin.

In the multiple regression model for log IL-6, significant independent contributions were provided by weight and 'Other' racial origin ($P \leq .001$, $R^2 = 0.125$): Log IL-6 expected = 5.496581 + 0.004763 × weight (in kg) + 0.309845 × 'Other' racial origin.

In the multiple regression model for log endothelin, significant independent contributions were provided by black racial origin and parity ($P \leq .001$, $R^2 = 0.138$): Log endothelin expected = 2.297770 + 0.076133 × black racial origin + 0.073548 × parity.

In the multiple regression model for log TNF-α, there were no significant independent contributions provided by maternal characteristics.

3.2.2 | Comparison of multiples of the median between groups

In women with CH, compared with the normotensive controls there was a significantly higher first trimester serum

concentration of endothelin but not of VCAM, IL-6 and TNF-α (Table 2, Figure 1). Within the cohort of women with CH, those who developed superimposed PE, compared with those who did not, had a higher first trimester serum concentration of VCAM, but not of endothelin, IL-6 or TNF-α (Table 2, Figure 1). Within the cohort of women with CH who developed superimposed PE, those who required delivery <37 weeks' gestation, compared with those who delivered ≥37 weeks' gestation, had higher first trimester serum concentration of VCAM (P = .012) but not of endothelin, IL-6 or TNF-α (Nzelu D, Dumitrascu-Biris D, Karampitsakos T, Nicolaides KH, Kametas NA, unpublished data).

3.2.3 | Performance of screening

Univariate logistic regression analysis demonstrated that MoM log VCAM was the only inflammatory mediator predictive of superimposed PE. The logistic regression model was logitPE = −1.063750 + 2.224226 × MoM log VCAM ($P \leq .01$, Nagelkerke R^2 0.015). The corresponding area under the ROC curve for VCAM in the prediction of PE was 0.537 (95% CI 0.487-0.587) (Figure 2).

3.2.4 | Sensitivity analysis

Matched-samples analysis demonstrated identical results to those presented above both for comparison of maternal and pregnancy characteristics (Table S1) and inflammatory mediators (Table S2). For the performance of screening, conditional logistic regression analysis demonstrated that MoM Log VCAM was the only inflammatory mediator predictive of the development of PE (odds ratio [OR] 6.025, 95% confidence interval [CI] 1.34-27.07, P = .01). In contrast, MoM Log endothelin (P = .13), IL6 (P = .69) and TNF-a (P = .35) were not predictive of the development of PE.

4 | DISCUSSION

The findings of this study demonstrate that at 11^{+0} to 13^{+6} weeks' gestation, in women with CH compared with the normotensive controls, serum levels of endothelin were increased but TNF-α, IL-6 and VCAM were not significantly different. Within the group of women with CH, only serum levels of VCAM were higher in those who developed superimposed PE compared with those who did not. However, in women with CH, first trimester serum levels of VCAM are poorly predictive of superimposed PE.

In normal pregnancy, the current literature has demonstrated a doubling in the production of IL-6[13] and TNF-α[14] in the early first trimester when compared with non-pregnant controls. It has been suggested that both cytokines have a major role in the paracrine regulation of placental development and hormone production.[2] Conversely, first trimester maternal endothelin levels are approximately halved when compared with non-pregnant controls, which is considered to be a protective mechanism against the vasoconstrictive actions of endothelin.[15]

Outside of pregnancy, TNF-α has been shown to induce structural as well as functional alterations in endothelial cells, enhancing the formation and release of endothelin, a potent vasoconstrictor, and downregulating the production of endothelial nitric oxide synthase.[7] Significantly higher levels of endothelin have been demonstrated in non-pregnant patients with moderate to severe hypertension, which, through the effects of endothelin on vascular remodeling, has been shown to lead to the development and progression of atherosclerosis.[16] Endothelin is also known to increase the expression of other inflammatory cytokines, such as IL-6, and cell adhesion molecules, such as VCAM. Increased expression of VCAM and IL-6 has been observed in patients with primary hypertension[17,18] and plays an important role in the early stages of hypertensive vascular injury and atherogenesis.[19,20] Thus, the endothelial dysfunction associated with many forms of hypertension including PE may in part also be mediated through these pro-inflammatory cytokines.

There is extensive literature demonstrating raised concentrations of IL-6, TNF-α, VCAM and endothelin in pregnancies already

TABLE 2 Comparison of maternal serum endothelin, IL-6, TNF-α and VCAM between normotensive controls, women with chronic hypertension who did not develop superimposed preeclampsia and those who did

Biomarkers	Controls (n = 142)	Chronic hypertension		Overall P value
		No preeclampsia (n = 448)	Preeclampsia (n = 202)	
Endothelin MoM, median (IQR)	1.002 (0.917-1.093)[a,b]	1.031 (0.952-1.127)	1.053 (0.954-1.152)	.015
IL-6 MoM, median (IQR)	0.993 (0.872-1.117)	0.935 (0.809-1.079)	0.927 (0.799-1.075)	.133
TNF-α, median (IQR)	1.336 (1.255-1.420)	1.345 (1.264-1.450)	1.352 (1.248-1.481)	.427
VCAM MoM, median (IQR)	0.999 (0.939-1.057)	0.979 (0.914-1.047)[c]	0.998 (0.932-1.084)	.003

Abbreviations: IL-6, interleukin-6; IQR, interquartile range; MoM, multiples of the median; TNF-α, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule.

[a]Statistically significant difference between the controls and the group with chronic hypertension who did not develop preeclampsia.

[b]Statistically significant difference between the controls and the group with chronic hypertension who developed preeclampsia.

[c]Statistically significant difference in the chronic hypertension group between those who developed preeclampsia and those who did not.

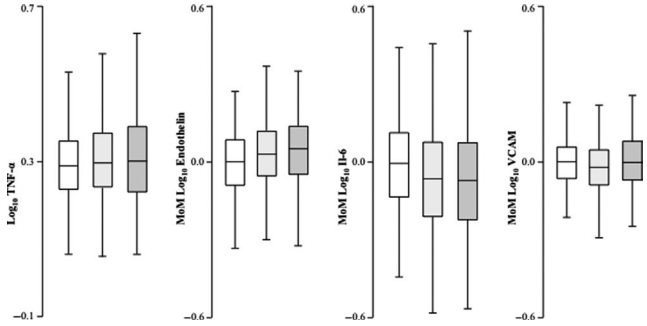

FIGURE 1 Serum levels of Log TNF-α and MoM Log endothelin, MoM Log IL-6 and MoM Log VCAM in controls (white box), women with chronic hypertension who did not develop preeclampsia (light gray box) and women with chronic hypertension who developed preeclampsia (dark gray box). TNF-α, tumor necrosis factor-alpha; MoM, multiples of the median; IL-6, interleukin-6; VCAM, vascular cell adhesion molecule

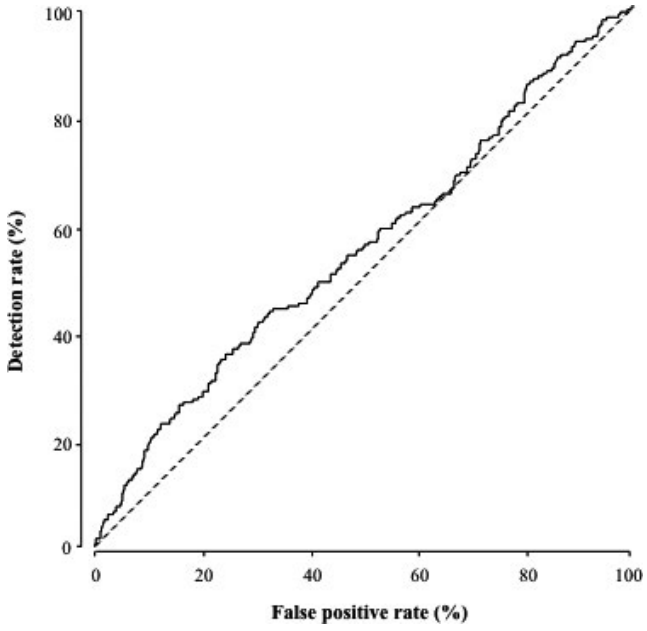

FIGURE 2 Receiver operating characteristic curves for the prediction of superimposed preeclampsia by MoM Log VCAM. MoM, multiples of the median; VCAM, vascular cell adhesion molecule

complicated by PE. Early atherosclerotic-like lesions have been demonstrated in the spiral arteries of pregnancies complicated by PE, particularly when preterm.[6,21] As previously mentioned, IL-6, TNF-α, VCAM and endothelin are all involved in the inflammatory cascade that leads to the development of endothelial dysfunction and atherosclerosis outside of pregnancy.[7,19] It has been proposed that, in PE, upregulation of these inflammatory mediators lead to the development of similar lesions within the feto-placental circulation and, systemically, lead to the clinical manifestation of the disease.[21] However, it has not yet been fully determined whether this inflammatory process predates the placental impairment or whether it is a consequence of it.

In contrast to those later in pregnancy, results of the studies in the general obstetric population evaluating first trimester concentrations of these circulating cytokines are more conflicting. Seven studies have investigated maternal TNF-α levels in the first trimester from a total of 144 normotensive women destined to develop PE and 692 with uncomplicated pregnancies.[22-25] Of these, two studies[22] reported an increase in first trimester serum TNF-α levels in women destined to develop PE, and the remaining five studies[22-25] reported no significant differences. Three studies investigated first trimester serum IL-6 from a total of 80 women destined to develop PE and 558 with uncomplicated pregnancies and found no significant differences.[23,25,26] Finally, two studies[15,27] have reported on first trimester serum endothelin levels in normotensive women. One study demonstrated significantly higher endothelin in women who subsequently developed PE, this increase being proportional to the severity of the disease.[27] The second study found a positive correlation between first trimester endothelin levels and systolic and diastolic blood pressures within the normal range in women with uncomplicated pregnancies.[15]

To our knowledge, there are no studies evaluating first trimester serum endothelin, IL-6, TNF-α or VCAM in women with CH. However, as with our findings, in 24 women with insulin-dependent diabetes, endothelin was increased in early pregnancy when compared with healthy controls.[28] Furthermore, the endothelin levels did not differ between diabetic women who subsequently developed PE and those who did not.[28] Diabetes and hypertension share a common pathophysiological pathway, in that endothelial dysfunction is a predominant feature.[8] In pregnancy, the two comorbidities also demonstrate a similar decrease in first trimester production of placental growth factor (PLGF) indicative of abnormal placentation.[29] We have previously shown that the decrease in first trimester PLGF is significantly greater in women with CH who develop PE compared with those who do not.[11] In addition, Panaitescu et al demonstrated that in women with CH who develop PE, a smaller deviation from normal in PLGF was observed.[30] Altogether, this suggests that a smaller contribution of abnormal placentation is needed to trigger PE in women with preexisting endothelial dysfunction, such as in those with CH.[30]

The incidence of PE in women with CH is about 20%.[1] Effective first trimester screening would allow for the early identification of women with CH who are at high risk of developing superimposed PE to enable appropriate pharmacological interventions and antenatal surveillance. Although we found that first trimester endothelin was elevated in women with CH compared with controls, there was no difference between those who developed superimposed PE and those who did not. This suggests that endothelin, as a marker of endothelial dysfunction, on its own is unlikely to be useful in stratifying the care of women with CH. Furthermore, we have previously reported that, in women with CH, PLGF performs poorly in the prediction of PE. [11]

It may be that, unlike in the general obstetric population, in women with CH, the approach to screening and prophylaxis for PE needs to take into account the multifactorial contributions of both

preexisting endothelial dysfunction, exacerbated by the physiological burden of pregnancy, and abnormal placentation. For example, the use of low-dose aspirin for the prophylaxis of PE in women at high risk for PE reduces the risk of preterm PE by >60%.[31] However, the beneficial effect of aspirin for the prophylaxis of PE was not observed in women with CH.[31] It is possible that aspirin, given to improve placentation, is not able to exert as significant an effect on the degree of placental impairment in women with CH when compared with those without. Therefore, future research should focus on other prophylactic strategies, such as stricter control of blood pressure.

The strengths of this study are examination of a large population of women with CH recruited in the first trimester of pregnancy and followed up with a standardized policy for strict control of blood pressure throughout pregnancy. Furthermore, the exclusion of women with underlying renal or liver disease at booking has reduced the heterogeneity of the population, thereby avoiding bias in the diagnosis of PE.

There are inherent methodological limitations to the measurement of TNF-α and IL-6 that we could not take into account in our analysis.[32] The circadian rhythm, body mass index, diet as well as emotional stress have all been shown to affect circulating levels of IL-6 and TNF-α.[32] Considering these factors, it may be that our study was not adequately powered to detect small differences in TNF-α and IL-6 between the groups.

5 | CONCLUSIONS

Women with CH have increased serum endothelin in the first trimester of pregnancy and those who develop superimposed PE have higher levels of VCAM, but none of the inflammatory mediators provided useful prediction of superimposed PE.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcomes: a cohort study. *Ultrasound Obstet Gynecol*. 2017;50:228-235.
2. Opsjøn S-L, Wathen NC, Tingulstad S, et al. Tumor necrosis factor, interleukin-1, and interleukin-6 in normal human pregnancy. *Am J Obstet Gynecol*. 1993;169:397-404.
3. Damsky CH, Fitzgerald ML, Fisher SJ. Distribution patterns of extracellular matrix components and adhesion receptors are intricately modulated during first trimester cytotrophoblast differentiation along the invasive pathway, in vivo. *J Clin Invest*. 1992;89:210-222.
4. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol*. 1999;180:499-506.
5. Wolff K, Nisell H, Carlström K, et al. Endothelin-1 and big endothelin-1 levels in normal term pregnancy and in preeclampsia. *Regul Pept*. 1996;67:211-216.
6. Szarka A, Rigo J Jr, Lazar L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. *BMC Immunol*. 2010;11:59.
7. LaMarca BB, Cockrell K, Sullivan E, Bennett W, Granger JP. Role of endothelin in mediating tumor necrosis factor-induced hypertension in pregnant rats. *Hypertension*. 2005;46:82-86.
8. Schiffrin EL, Deng LY, Sventek P, Day R. Enhanced expression of endothelin-1 gene in resistance arteries in severe human essential hypertension. *J Hypertens*. 1997;15:57-63.
9. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;4:97-104.
10. National Institute for Health and Clinical Excellence. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. London: NICE; 2010
11. Nzelu D, Biris D, Karampitsakos T, Nicolaides KK, Kametas NA. First trimester serum angiogenic and anti-angiogenic factors in women with chronic hypertension for the prediction of preeclampsia. *Am J Obstet Gynecol*. 2019. https://doi.org/10.1016/j.ajog.2019.10.101
12. Maršál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843-848.
13. Austgulen R, Lien E, Liabakk NB, Jacobsen G, Arntzen KJ. Increased levels of cytokines and cytokine activity modifiers in normal pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1994;57:149-155.
14. Arntzen KJ, Liabakk NB, Jacobsen G, Espevik T, Austgulen R. Soluble tumor necrosis factor receptor in serum and urine throughout normal pregnancy and at delivery. *Am J Reprod Immunol*. 1995;34:163-169.
15. Lygnos MC, Pappa KI, Papadaki HA, et al. Changes in maternal plasma levels of VEGF, bFGF, TGF-beta1, ET-1 and sKL during uncomplicated pregnancy, hypertensive pregnancy and gestational diabetes. *Vivo*. 2006;20:157-163.
16. Hasdai D, Lerman A. The atherogenic potential of endothelin. *Coron Artery Dis*. 1995;6:901-904.
17. DeSouza CA, Dengel DR, Macko RF, Cox K, Seals DR. Elevated levels of circulating cell adhesion molecules in uncomplicated essential hypertension. *Am J Hypertens*. 1997;10:1335-1341.
18. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. *J Hum Hypertens*. 2005;19:149-154.
19. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol*. 2007;49:2379-2393.
20. Huber SA, Sakkinen P, Conze D, Hardin N, Tracy R. Interleukin-6 exacerbates early atherosclerosis in mice. *Arterioscler Thromb Vasc Biol*. 1999;19:2364-2367.
21. Staff AC, Johnsen GM, Dechend R, Redman CWG. Preeclampsia and uteroplacental acute atherosis: immune and inflammatory factors. *J Reprod Immunol*. 2014;101–102:120-126.
22. Lau SY, Guild S-J, Barrett CJ, et al. Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. *Am J Reprod Immunol*. 2013;70:412-427.
23. Eneroth E, Remberger M, Vahlne A, Ringden O. Increased serum concentrations of interleukin-2 receptor in the first trimester in

women who later developed severe preeclampsia. *Acta Obstet Gynecol Scand*. 1998;77:591-593.
24. Salazar Garcia MD, Mobley Y, Henson J, et al. Early pregnancy immune biomarkers in peripheral blood may predict preeclampsia. *J Reprod Immunol*. 2018;125:25-31.
25. Tangerås LH, Austdal M, Skråstad RB, et al. Distinct first trimester cytokine profiles for gestational hypertension and preeclampsia. *Arterioscler Thromb Vasc Biol*. 2015;35:2478-2485.
26. Freeman DJ, McManus F, Brown EA, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. *Hypertension*. 2004;44:708-714.
27. Shaarawy M, Abdel-Magid AM. Plasma endothelin-1 and mean arterial pressure in the prediction of pre-eclampsia. *Int J Gynaecol Obstet*. 2000;68:105-111.
28. Wolff K, Carlstrom K, Fyhrquist F, Hemsen A, Lunell NO, Nisell H. Plasma endothelin in normal and diabetic pregnancy. *Diabetes Care*. 1997;20:653-656.
29. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol*. 2015;45:591-598.
30. Panaitescu AM, Akolekar R, Kametas N, Syngelaki A, Nicolaides KH. Impaired placentation in women with chronic hypertension who develop pre-eclampsia. *Ultrasound Obstet Gynecol*. 2017;50:496-500.
31. Poon LC, Wright D, Rolnik DL, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. *Am J Obstet Gynecol*. 2017;217:585.e1–585.e5.
32. Zhou X, Fragala MS, McElhaney JE, Kuchel GA. Conceptual and methodological issues relevant to cytokine and inflammatory marker measurements in clinical research. *Curr Opin Clin Nutr Metab Care*. 2010;13:541-547.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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