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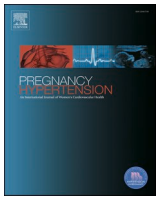

Circulating concentrations of pro-inflammatory cytokines in preeclampsia with varying disease severity

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ABSTRACT

Objectives: To assess whether plasma concentrations of the circulating inflammatory proteins Interleukin-6 (IL-6), Vascular Cell Adhesion Molecule-1 (VCAM-1) and C-Reactive Protein (CRP) are increased in women with preeclampsia with end-organ complications, compared with women with preeclampsia without end-organ complications.

Study design: We used samples from a large prospective biobank collection (Preeclampsia Obstetric Adverse Event biobank), and two large, randomized preeclampsia therapeutic treatment trials. All samples were collected in Cape Town, South Africa. The last plasma sample collected prior to birth was analyzed for IL-6, VCAM-1 and CRP concentrations. We categorized cases according to disease severity and compared circulating levels of these analytes. Covariate adjustment was performed.

Results: 183 women were included. Compared with women without end-organ complications (n = 119), those with preeclampsia with two or more end-organ complications (n = 15) had a 4.9-fold (95 % CI, 1.81–13.09, p = 0.001) increase in IL-6 and a 1.7-fold (95 % CI, 1.11–2.72, p = 0.012) increase in VCAM-1 plasma concentrations. Comparing women with two or more end-organ complications to those with one end-organ complication (n = 49), plasma concentrations of IL-6 were 3.2-fold (95 % CI, 1.18–8.39, p = 0.018) increased, while there was no statistically significant difference for VCAM-1 (1.2-fold higher, 95 % CI, 0.79–1.91, p = 0.50). Plasma concentrations of CRP did not differ between the groups.

Conclusions: Plasma concentrations of IL-6 and VCAM-1, but not CRP, were increased among women with preeclampsia and end-organ complications, compared with women without end-organ complications. IL-6 and VCAM-1 could be drivers of disease in preeclampsia and potentially useful to identify women at high risk of severe disease.

1. Background

Preeclampsia affects approximately 5 % of all pregnancies and is responsible for more than 60,000 maternal deaths annually [1,2]. It is a pregnancy disorder characterized by hypertension with end-organ dysfunction that can vary from mild hypertension and proteinuria to potentially lethal complications [3]. End-organ complications that occur with severe disease include eclampsia, stroke, coma, pulmonary edema,

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CRP, C-Reactive Protein; DIC, Disseminated Intravascular Coagulation; ER, extended-release; HELLP, Hemolysis Elevated Liver enzymes Low Platelets; IL-6, Interleukin-6; ISSHP, International Society for the Study of Hypertension in Pregnancy; LOD, lowest optical density; PIE, Preeclampsia Intervention with Esomeprazole; PI2, Preeclampsia Intervention 2; PROVE, Preeclampsia Obstetric Adverse Events; VCAM-1, Vascular Cell Adhesion Molecule-1.

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left ventricular failure, renal impairment, Disseminated Intravascular Coagulation (DIC), impaired liver function and Hemolysis Elevated Liver enzymes Low Platelets (HELLP) syndrome [1,3].

Preeclampsia is associated with a systemic inflammatory response. There is increased chronic peripheral and placental inflammation leading to increased plasma concentrations of inflammatory biomarkers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Vascular Cell Adhesion Molecule-1 (VCAM-1) [4–12]. Previous studies have been small with outcomes mainly of severe hypertension without end-organ complications. IL-6 and VCAM-1 concentrations seem increased in preeclampsia with severe features [13–18]. The results for CRP are conflicting with some finding increased levels with severe features and others not [15,18–23]. There is uncertainty about whether these biomarkers are drivers of disease and associated with disease severity.

We therefore aimed to assess whether plasma concentrations of IL-6, VCAM-1 and CRP were increased in a large cohort of women with preeclampsia with end-organ complications (severe disease) versus those with preeclampsia and no end organ complications (hypertension and excessive proteinuria only).

2. Materials and methods

2.1. Study cohorts

Women recruited to the Preeclampsia Obstetric Adverse Events (PROVE) Biobank, the Preeclampsia Intervention with Esomeprazole (PIE) trial and the Preeclampsia Intervention 2 (PI2) trial between 2016 and 2020 at Tygerberg Hospital in Cape Town, South Africa were included [24–26]. The PROVE biobank (ISRCTN10623443) aims to facilitate research in the field of preeclampsia [24]. The PIE (PACTR201504000771349) and PI2 (PACTR201608001752102) trials were randomized controlled trials assessing novel therapeutics to prolong gestation in women diagnosed with preterm preeclampsia (between 26 and 32 gestational weeks) [25,26]. In the PIE trial, women were randomized to 40 mg esomeprazole daily or placebo and in the PI2 trial, women were randomized to up to 1 g metformin extended-release (ER) or placebo three times a day (up to 3 g total).

2.2. Inclusion and exclusion criteria

Women with preeclampsia with a singleton pregnancy recruited to PROVE, PIE or PI2 were eligible for inclusion if they had blood samples collected before delivery. Preeclampsia was defined according to International Society for the Study of Hypertension in Pregnancy (ISSHP) definition, but significant proteinuria was required for the diagnosis (protein creatinine ratio $\geq$30 mg/mmol or $\geq$0.3 g protein in 24-hour urine collection or urine dipstick >1+ on more than one occasion) [27]. Superimposed preeclampsia was diagnosed when a woman with chronic hypertension lost blood pressure control in combination with a development of significant proteinuria. We excluded women from the intervention trials who received esomeprazole or metformin ER as these drugs may have influenced concentrations of inflammatory markers.

2.3. Groups

Women with preeclampsia were categorized into three groups: preeclampsia without end-organ complications, preeclampsia with one end-organ complication and preeclampsia with two or more end-organ complications from different organ systems. Preeclampsia without end-organ complications was defined as hypertension (of any degree) and significant proteinuria, without other end-organ impairment. Preeclampsia with one end-organ complication was defined as hypertension, significant proteinuria and one of following: cerebral complications, cardiorespiratory complications, renal complications or liver/coagulation system complications. Severe hypertension (systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$110 mmHg) could be present in any of the groups. Cerebral complications included eclampsia (generalized tonic clonic seizure in a woman with preeclampsia, in the absence of other causes of seizures), stroke (clinical symptoms with confirmatory computer tomography findings) and coma (Glasgow Coma Score < 13). Cardiorespiratory complications included pulmonary edema (worsening dyspnea and auscultation of fine bibasal inspiratory crackles, together with either features of pulmonary edema on chest x-ray or oxygen saturation $\leq$90 %) and left ventricular failure (ejection fraction <40 % on echocardiography). Renal complications included renal impairment (serum creatinine >120 μmol/L). Liver/coagulation system complications included DIC (plasma international normalized ratio > 1), impaired liver function (aspartate aminotransferase (AST) or alanine aminotransferase > 500 IU/L in plasma) and HELLP syndrome (blood platelet count $<100 \times 10^9$/L, plasma AST > 70 IU/L and hemolysis as demonstrated by serum lactate dehydrogenase > 600 U/L or hemolysis on a peripheral blood smear).

2.4. Sample collection and biomarker analysis

Whole blood samples were collected in 9 ml ethylenediaminetetraacetic acid tubes and were centrifuged, aliquoted and frozen at −70 degrees Celsius. Samples were shipped to the Translational Obstetrics Group, University of Melbourne in Australia, for analyses. IL-6, VCAM-1 and CRP concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, USA) according to manufacturer's instructions. Calibrations were run in duplicate. Samples were run in singleton. Samples were diluted 1:3,000 for VCAM-1 analyses and 1:50,000 for CRP analyses. IL-6 samples were not diluted. Lowest optical density (LOD) was 4.69 pg/ml for IL-6, 23,430 pg/ml for VCAM-1 and 390,500 pg/ml for CRP. One quality control was run across all plates. The inter-assay coefficient of variation was 26.9 % for CRP, 11.4 % for IL-6 and 9.4 % for VCAM-1. Laboratory technicians were blinded to groups.

2.5. Data collection

Baseline data were retrieved from electronic REDCap (Research Electronic Data Capture databases), merged into an Excel spreadsheet (version 16.7, Microsoft Corporation, Redmond, WA, USA), and was double-checked for accuracy [28].

2.6. Statistical methods

Descriptive data are presented as means and standard deviations or medians and interquartile ranges for numeric variables. Categorical variables are presented as numbers and percentages. Concentrations of biomarkers are illustrated by scatter plots.

Comparisons of biomarkers between groups were performed using Welch's unequal variances ANOVA (unadjusted) and Welch's ANCOVA (adjusted) on log-transformed values. Log-transformation was used to account for the skewed (non-normal) distribution of the biomarkers. Differences in biomarkers between groups were presented as fold-changes with 95 % confidence intervals. Pairwise comparisons between groups were performed with the Tukey-Kramer procedure to account for multiple testing. All analyses were performed unadjusted and adjusted for confounders which included gestation at sampling, time from sampling to delivery, maternal age and body mass index (BMI).

Missing values due to concentrations below detectable limit were replaced with the LOD. Reads below the LOD were kept as recorded in the primary analysis. A sensitivity analysis was also conducted, in which missing values and values below the LOD were treated as left-censored at the LOD.

All tests were two-sided and performed at 5 % significance level. Statistical analyses were performed using SPSS version 28.0.1 (SPSS, PASW statistics, Armonk, NY: IBM Corp) and SAS version 9.4 (SAS Institute, Cary, NC, USA). Scatter plots were created in Prism version

9.3.1 for Mac (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Study population

We investigated 183 women and a flowchart of the population is described in Fig. 1. 119 (65 %) had preeclampsia without end-organ complications, 49 (27 %) had one end-organ complication (more severe clinical disease) and 15 (8 %) had two or more end-organ complications (the most severe clinical disease).

Women with end-organ complications were younger, had a higher BMI and were more likely to be nulliparous (Table 1). Time from sampling to delivery was shorter in women with one end-organ complication. Women with two or more end-organ complications were more likely to have a stillborn child.

3.2. Circulating inflammatory biomarkers

Though IL-6 plasma concentrations were 1.5-fold (95 % Confidence Interval (CI) 0.79–3.01, p = 0.26) increased in women with one end-organ complication, compared with women with no end-organ complications, the difference was not statistically significant in the adjusted analyses. Preeclampsia with two or more end-organ complications was associated with a 4.9-fold (95 % CI, 1.81–13.09, p = 0.001) increase in IL-6 when compared with women without end-organ complications. Comparing women with two or more end-organ complications to those with one end-organ complication, plasma concentrations of IL-6 were 3.2-fold increased (95 % CI, 1.18–8.39, p = 0.018) (Table 2, Fig. 2, Supplemental Table S1). In the sensitivity analysis, which considered missing values and values below the LOD as left-censored, differences in IL-6 between groups remained (Supplemental Table S2). In this sensitivity analysis, women with preeclampsia with one end-organ complication had a borderline significant 2.2-fold increase of IL-6 compared with preeclampsia without end-organ complications (95 % 0.96–4.83, p = 0.066). When excluding women with superimposed preeclampsia,

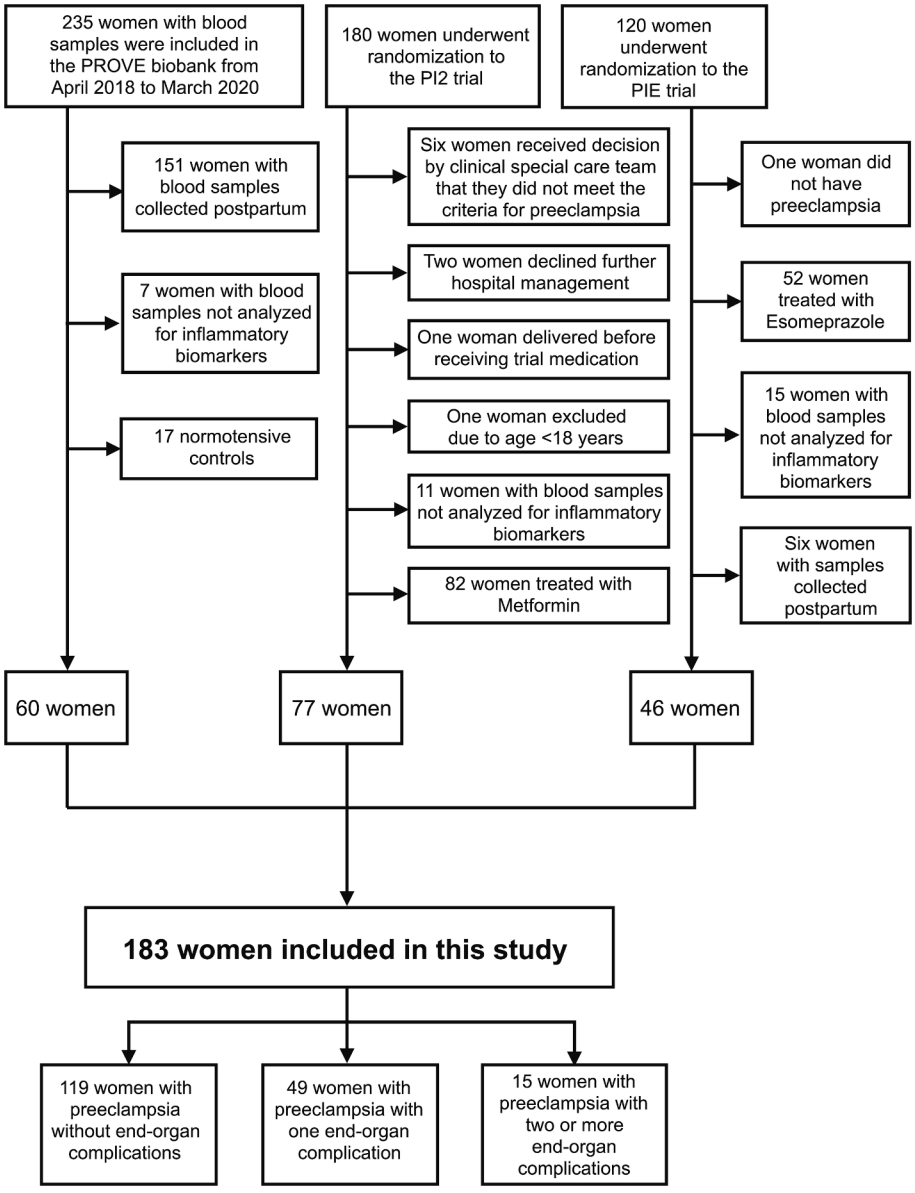

Fig. 1. Flowchart of the study population. Abbreviations: PROVE, Preeclampsia Obstetric Adverse Events; PI2, Preeclampsia Intervention 2; PIE, Preeclampsia Intervention with Esomeprazole.

Table 1
Background characteristics by subtype of preeclampsia.

	Preeclampsia without end-organ complications	Preeclampsia with one end-organ complication	Preeclampsia with two or more end-organ complications
n	**119**	**49**	**15**
At baseline			
Age, years	29.5 [6.4]	24.1 [6.4]	22.9 [4.3]
Nulliparous	40 (33.6)	27 (55.1)	11 (73.3)
BMI, kg/m^2	30.5 [6.9]	28.1 [7.0]	25.4 [4.1]
Missing	2 (1.7)	5 (10.2)	1 (6.7)
HIV positive	30 (25.2)	8 (16.3)	2 (13.3)
Chronic hypertension	38 (31.9)	7 (14.3)	2 (13.3)
Smoking during pregnancy	15 (12.6)	10 (20.4)	3 (20.0)
Study recruited to			
PROVE	15 (12.6)	31 (63.3)	14 (93.3)
PI2	65 (54.6)	11 (22.4)	1 (6.7)
PIE	39 (32.8)	7 (14.3)	0 (0.0)
After inclusion			
Highest systolic BP, mmHg	170 [15]	176 [20]	172 [17]
Highest diastolic BP, mmHg	104 [12]	110 [15]	106 [14]
Gestation at sampling, weeks	31.1 [3.2]	32.0 [4.0]	31.3 [3.5]
Missing	2 (1.7)	0 (0.0)	0 (0.0)
Gestation at delivery, weeks	32.0 [2.9]	32.2 [3.9]	32.0 [3.3]
Days between sampling and delivery	5.9 [9.1]	1.3 [3.1]	4.2 [7.8]
Missing	2 (1.7)	0 (0.0)	0 (0.0)
Mode of birth			
Vaginal	17 (14.3)	11 (22.4)	6 (40.0)
Elective/non urgent CS	22 (18.5)	5 (10.2)	0 (0.0)
Emergency CS	80 (67.2)	33 (67.3)	9 (60.0)
Liveborn	116 (97.5)	46 (93.9)	9 (60.0)
Birthweight, g	1510 [662]	1742 [882]	1579 [734]
Maternal complications			
Eclampsia	0 (0.0)	24 (49.0)	11 (73.3)
Stroke	0 (0.0)	1 (2.0)	1 (6.7)
Coma	0 (0.0)	1 (2.0)	2 (13.3)
Pulmonary edema	0 (0.0)	9 (18.4)	3 (20.0)
Left ventricular failure	0 (0.0)	1 (2.0)	0 (0.0)
Severe renal failure	0 (0.0)	2 (4.1)	7 (46.7)
HELLP	0 (0.0)	12 (24.5)	10 (66.7)
DIC	0 (0.0)	0 (0.0)	5 (33.3)
Elevated liver enzymes	0 (0.0)	0 (0.0)	1 (6.7)

For continuous variables, data are presented as mean [standard deviation]. For categorical variables, data are presented as number (percentage). Abbreviations: BMI, Body Mass Index; BP, Blood Pressure; CS, Caesarean Section; DIC, Disseminated Intravascular Coagulation; HELLP, Hemolysis Elevated Liver enzymes Low Platelets; HIV, Human Immunodeficiency Virus; PI2, Preeclampsia Intervention 2; PIE, Preeclampsia Intervention with Esomeprazole; PROVE, Preeclampsia Obstetric Adverse Events.

differences in IL-6 between groups remained (Supplemental Table S3-S4).

Women with one end-organ complication had 1.4-fold increased plasma concentrations of VCAM-1 (95 % CI, 1.03–1.96, p = 0.032) compared with women with no end-organ complications. Women with two or more end-organ complications had 1.7-fold increased plasma concentrations of VCAM-1 (95 % CI, 1.11–2.72, p = 0.012) compared with women without end-organ complications. There was no difference in VCAM-1 concentrations between women with one or two or more end-organ complications (Table 2, Fig. 2, Table S1). When excluding women with superimposed preeclampsia, differences in VCAM-1 between groups remained (Supplemental Table S3).

There were no differences in plasma concentrations of CRP between groups after adjustment for confounders (Table 2, Fig. 2, Table S1).

4. Discussion

4.1. Principal findings

Among women with preeclampsia, IL-6 and VCAM-1 plasma concentrations were increased for those with end-organ complications and thus, those with more severe disease. CRP plasma concentrations did not differ between women with preeclampsia of different severity.

4.2. Results in context

We showed that increased IL-6 concentrations were associated with the degree of end-organ involvement in preeclampsia, or worsening severity of disease. Others have shown increased concentrations with increasing disease severity, but these studies included only a small number with severe end-organ disease and most studies included any organ dysfunction and severe hypertension as indicators of severity. In addition, our study is at least twice as large as earlier published data [13–15]. Others have not shown an increase in IL-6 concentration with disease severity, but these studies were also limited by the definition of disease severity. Their definition of severe disease included severe hypertension (blood pressure ≥ 160/110) and/or severe proteinuria (dipstick reading of 3–4 + proteinuria) and not end-organ injury [20–22]. Our study is the first to demonstrate that circulating IL-6 concentrations increased by number of end-organ complications irrespective of the presence of severe hypertension.

We found that increased VCAM-1 concentrations were associated with end-organ dysfunction in preeclampsia. Others have also shown increased levels in severe disease, but again, these studies only included a few cases with end-organ complications and most of the severe cases were severe hypertension or dipstick measurement of proteinuria ≥ 2+ [16–18]. Our study adds strength to this association as we have strict criteria for end-organ involvement.

We found no differences in CRP concentrations with end-organ complications. Others have shown both increased CRP concentrations and no difference in severe preeclampsia, but these studies included severe hypertension and other symptoms as severe features and not end-organ complications [15,18–23].

5. Strengths and limitations

Within our study, 35 % of women experienced one or more end-organ complications. This incidence of complications is greater than those of previous studies investigating inflammatory biomarkers. The large number of severe complications enabled us to investigate inflammatory biomarkers in severe disease, irrespective of severe hypertension. In addition, the analysis used to measure concentrations of inflammatory biomarkers in plasma is well established. Limitations include the large variation of time from sampling to delivery between women and groups. In women with no, one and two or more end-organ complications, time from sampling to delivery was 5.9 (standard deviation (SD) 9.1), 1.3 (SD 3.1) and 4.2 (SD 7.8) days, respectively. However, this was corrected for in the adjusted analyses. The high LOD in the IL-6 analysis is also a limitation as 52 % had an IL-6 concentration below detectable limit, most of which occurred in the group with no end-organ complications. Consequently, even stronger associations with IL-6 and the number of end-organ complications were observed in the sensitivity analysis where missing data below the LOD were treated as censored at the LOD.

Table 2
Fold-changes of inflammatory biomarkers between subgroups of preeclampsia, crude and adjusted for gestation at sampling, time from sampling to delivery, maternal age and BMI.

		IL-6		VCAM-1		CRP	
Subgroup	Reference	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Preeclampsia without end-organ complications (n = 119)	Preeclampsia without end-organ complications (n = 119)	1.00	1.00	1.00	1.00	1.00	1.00
Preeclampsia with one end-organ complication (n = 49)		2.56 (1.45–4.52) p < 0.001	1.54 (0.79–3.01) p = 0.26	1.55 (1.19–2.04) p < 0.001	1.42 (1.03–1.96) p = 0.032	2.66 (1.12–6.33) p = 0.024	1.50 (0.53–4.23) p = 0.61
Preeclampsia with two or more end-organ complications (n = 15)		7.22 (2.96–17.58) p < 0.001	4.87 (1.81–13.09) p = 0.001	1.99 (1.39–2.83) p < 0.001	1.74 (1.11–2.72) p = 0.012	1.32 (0.16–10.58) p = 0.94	0.61 (0.06–5.80) p = 0.85
Preeclampsia with one end-organ complication (n = 49)	Preeclampsia with one end-organ complication (n = 49)	1.00	1.00	1.00	1.00	1.00	1.00
Preeclampsia with two or more end-organ complications (n = 15)		2.82 (1.07–7.47) p = 0.034	3.15 (1.18–8.39) p = 0.018	1.28 (0.86–1.90) p = 0.30	1.23 (0.79–1.91) p = 0.50	0.49 (0.06–4.27) p = 0.70	0.41 (0.04–3.84) p = 0.59

Data are presented as fold-change (subgroup vs reference) with 95% confidence interval.
Unadjusted analyses were performed using Welch's ANOVA on log-transformed variables.
Adjusted analyses were performed using Welch's ANCOVA on log-transformed variables, adjusting for gestation at sampling, time from sampling to delivery, maternal age, and BMI.
Correction for multiple pairwise comparisons were performed using the Tukey-Kramer procedure.
Abbreviations: BMI, Body Mass Index; CRP, C-Reactive Protein; IL-6, Interleukin-6; VCAM-1, Vascular Cell Adhesion Molecule-1.

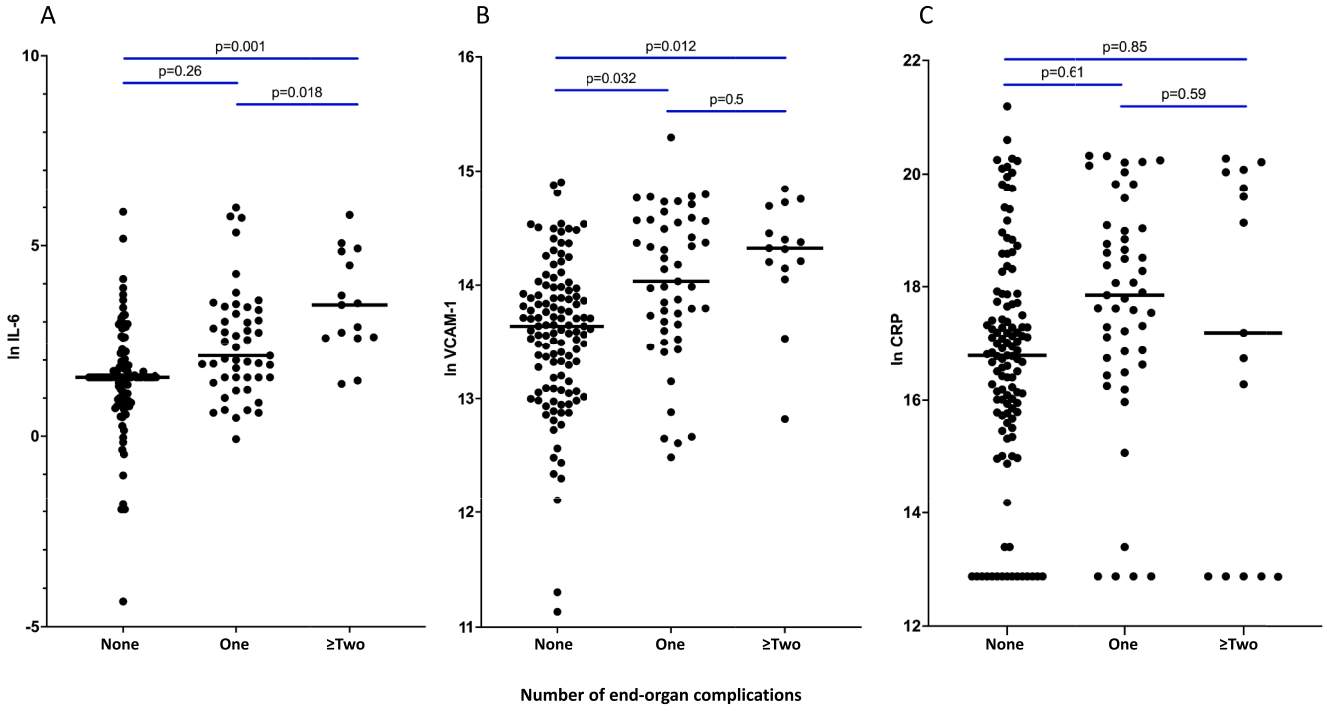

Fig. 2. Scatter plots of log-transformed plasma concentrations of IL-6 (A), VCAM-1 (B) and CRP (C). Abbreviations: CRP, C-Reactive Protein; IL-6, Interleukin-6; VCAM-1, Vascular Cell Adhesion Molecule-1.

5.1. Research implications

Concentrations of inflammatory biomarkers should also be tested in different end-organ complications to assess if any are associated with specific complications. Studies are needed to assess if these increased inflammatory biomarkers increase before the onset of end-organ complications. In addition, our findings of increased IL-6 and VCAM-1 warrant further mechanistic studies. These should investigate the role of inflammatory markers as disease drivers for endothelial dysfunction and potential targets for treatment in increasing severity of preeclampsia.

5.2. Clinical implications

If confirmed in prospective studies, the association between organ injury and increased concentrations of circulating inflammatory biomarkers may be useful in risk assessment, early detection, and diagnosis of end-organ complications in women with preeclampsia. They could be useful individually or incorporated into prediction models to increase the prognostic accuracy.

6. Conclusion

IL-6 and VCAM-1, but not CRP, were increased among women with

preeclampsia and end-organ complications. IL-6 and VCAM-1 may have an important role as a disease driver of preeclampsia. They could also have roles as candidate biomarkers for the diagnosis and possibly prediction of end-organ complications in preeclampsia.

7. Declarations

Ethics approval and consent to participate: The PROVE biobank, the PI2 trial and the PIE trial were approved by Stellenbosch University Health Research Ethics Committee (Federal Wide assurance number 00001372, Institutional Review Board number IRB0005239). The PROVE biobank's ethical approval was received on 28 February 2018 and is updated yearly (protocol number N18/03/034). The PI2 trial received ethical approval on 9 November 2016 (protocol number M16/09/037). The PIE trial received ethical approval on 7 November 2014 (protocol number M14/09/038). Informed consent has been signed by all participating women or their guardians.

Consent for publication: Not applicable.

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Authors' contributions: K.P. participated in the design of the study, managed the database, prepared tables and figures and drafted the manuscript. L.B. collected baseline data and blood samples, designed the study, and helped to draft the manuscript. R.H. conceived the study and conducted the immunoassays. S.T. and S.W. conceived the study and conducted the immunoassays. C.C. collected baseline data and blood samples, designed the study and helped to draft the manuscript. H.I. devised and performed the statistical analyses. E.L. collected baseline data. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2024.101168.

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