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Blood pressure as a risk factor for eclampsia and pulmonary oedema in pre-eclampsia

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ABSTRACT

Objective: We evaluated whether blood pressure and change in blood pressure measurements during pregnancy were associated with eclampsia or pulmonary oedema among women with pre-eclampsia.
Study design: Observational study of women with eclampsia, pre-eclampsia complicated by pulmonary oedema and pre-eclampsia without end-organ complications (pre-eclampsia controls) at a large referral center in Cape Town, South Africa.
Main outcome measures: Blood pressure measurements at presentation for antenatal care were compared to measurements after a diagnosis of pre-eclampsia. Mean blood pressures and changes in blood pressures were also calculated and compared between groups at different time points. A sub analysis including women who presented for antenatal care before 20 weeks of gestation was performed.
Results: When diagnosed with pre-eclampsia, women with pulmonary oedema had increased systolic blood pressures and women with eclampsia had increased diastolic blood pressures compared to pre-eclampsia controls.
There were no differences in blood pressure measurements in early pregnancy between women who later developed eclampsia or pulmonary oedema compared to pre-eclampsia controls.
Conclusion: Blood pressure measurements in early pregnancy do not seem useful as a risk factor for the development of eclampsia or pulmonary oedema among women diagnosed with pre-eclampsia. Increased systolic or diastolic pressure at diagnosis of pre-eclampsia may be useful as a risk factor for the development of pulmonary oedema or eclampsia. Further research is needed to confirm these findings.

1. Introduction

Pre-eclampsia, a pregnancy-specific disorder defined as the development of de-novo hypertension and end organ dysfunction after 20 weeks of gestation, complicates about 5% of all pregnancies [1]. It is considered the underlying cause of 10–15% of all maternal deaths with the majority of these deaths being related to cerebral complications or pulmonary oedema [2–4]. Eclampsia is diagnosed when generalized tonic-clonic seizures occur after 20 weeks of gestation in the absence of other underlying pathology [5]. Pulmonary oedema is characterized by fluid retention in the alveoli and is diagnosed by characteristic features on chest X-ray in combination with symptoms of dyspnea and orthopnea and in some cases respiratory failure.

Eclampsia can occur antepartum (38–52%), intrapartum (18–35%) or postpartum (11–44%) [6]. It is often preceded by hypertension and proteinuria, but may be the first manifestation of pre-eclampsia with approximately 15% of women not presenting with hypertension before an eclamptic event [7]. Magnesium sulphate halves the risk for eclampsia [8], but identifying who benefits from prophylaxis is challenging [9]. There are currently no reliable predictors to assist clinicians in identifying which women are at risk for eclampsia [10]. A quarter of pregnant women will have normal blood pressure values in the week

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preceding the onset of eclampsia [11] and the degree of hypertension is not always accurate in predicting who will develop eclampsia [10].

Pre-eclampsia complicated by pulmonary oedema accounts for up to 50% of maternal deaths related to pre-eclampsia [12]. The cause of pulmonary oedema in pre-eclampsia is most likely a combination of escalating hydrostatic pressure due to increased afterload and left ventricular diastolic dysfunction, capillary leaking and interstitial oedema [12–14]. A mainstay of treatment is strict blood pressure control to decrease afterload [12]. No studies have assessed if blood pressure at first presentation or blood pressure measurements in early pregnancy may be risk factors for the development of pulmonary oedema.

If blood pressure measurements at pregnancy baseline and or blood pressure trends were associated with the development of eclampsia and or pulmonary oedema, it could help predict those at highest risk for the most severe complications. We therefore set out to investigate if blood pressure measurements in early pregnancy, the degree of blood pressure change or blood pressure measurements at time of this diagnosis of pre-eclampsia were risk factors for eclampsia or pulmonary oedema.

2. Materials and methods

2.1. Study design

This was an observational study comparing blood pressure measurements in women with eclampsia, pulmonary oedema and pre-eclampsia without organ complications (pre-eclampsia controls). We assessed blood pressure measurements from early pregnancy and blood pressure measurements at the time of the diagnosis of pre-eclampsia where women were divided in three groups, pre-eclampsia complicated by eclampsia, pre-eclampsia complicated by pulmonary oedema and pre-eclampsia controls.

2.2. Population

Data was obtained from the Pre-eclampsia Obstetric Adverse Events (PROVE) Biobank and Database at Tygerberg Hospital, Cape Town, South Africa (https://www.isrctn.com/ISRCTN10623443) [15]. Tygerberg Hospital is the largest referral hospital in the Western Cape Provence of South Africa. In 2018 there were 32 422 deliveries in the referral area, of which 8067 were considered high risk and delivered at Tygerberg. A large proportion of these high-risk pregnancies are complicated by pre-eclampsia and end-organ complications are common.

Pre-eclampsia was defined as the de novo development of hypertension with proteinuria after 20 weeks of gestation. A diagnosis of eclampsia was made when generalized tonic-clonic seizures occurred in the presence of underlying pre-eclampsia (before or after the seizure) with no other organic cause for the seizures. Pulmonary oedema was diagnosed when there was worsening dyspnoea, fine bibasal inspiratory crackles on auscultation and features of pulmonary oedema on chest X-ray, with underlying pre-eclampsia. Women with pre-eclampsia and severe hypertension (systolic measurement above 160 mm Hg and or a diastolic measurement above 110 mm Hg) were included in all groups. Exclusion criteria included underlying neurological disease, cardiac disease and pre-existing hypertension. We also excluded women with pregnancies complicated with pre-eclampsia with other organ involvement including renal failure, haemolysis elevated liver enzymes and low platelet (HELLP) syndrome, disseminated intravascular coagulation, liver rupture, stroke or intracerebral bleeding. All women who developed hypertension were started on antihypertensive treatment according to the Guidelines for Maternity Care in South Africa.

In order to explore blood pressure changes from pregnancy baseline to diagnosis, a sub-group analysis was performed for women that had blood pressures recorded before 20 gestational weeks.

2.3. Blood pressure measurements

Blood pressure measurements were taken with the woman either sitting or lying on her side, with her arm at the level of her heart and with an appropriately sized blood pressure cuff. The majority of first antenatal visit blood pressure measurements were recorded at Midwife led Obstetric Units (MOU) or other district (level 1) facilities. Blood pressures at the time of the diagnosis of pre-eclampsia or eclampsia may have been recorded at the MOUs, district hospitals or at Tygerberg Hospital. All blood pressure recordings were obtained from medical chart extraction. For some women with eclampsia, blood pressure measurements were recorded both before and after fit. For women with pulmonary oedema, all blood pressure measurements were recorded after diagnosis of pulmonary oedema.

2.4. Statistics

To detect a difference in booking systolic blood pressure with a power of 80 and an alpha error of 0.05, a sample size of 32 women in each group were needed to detect a difference between 120 and 127 mm Hg with a SD of 10 mm Hg.

Demographic and clinical characteristics are presented as means with standard deviations (SD) and percentages and were compared between groups by ANOVA and chi-square tests. Blood pressure levels are presented as means with SD and compared between groups by use of One-way ANOVA and pairwise comparisons with Bonferroni correction. To control for potential confounders, a robust multi-Way ANOVA (parameter estimates with robust standard error to adjust for differences in variance) was conducted with maternal age and maternal body mass index as continuous covariates and were presented as estimated marginal means with 95 % confidence interval (CI). Pre-eclampsia without pulmonary oedema or eclampsia was set as the reference group in pairwise comparisons. In all hypothesis tests, a p-value of less than 0.05 was considered statistically significant. Data and statistical analyses were performed using SPSS version 26.0 (SPSS; PASW statistics) for MAC software package.

2.5. Ethical approval

This study had ethical approval from the Stellenbosch University Human Research Ethics Committee (HREC Reference No: S19/11/283) and all participants signed informed consent.

3. Results

A total of 224 women were enrolled in PROVE Biobank and Database from April 2018 to December 2019. Of the 139 included in this study, 70 women had eclampsia, 31 had pre-eclampsia complicated by pulmonary oedema and 38 were pre-eclampsia controls. A subgroup analyses included 91 women that had their first antenatal visit before 20 weeks of gestation. A flowchart of the population is presented in Fig. 1.

3.1. Background characteristics

Maternal characteristics are presented in Table 1. Women who had eclampsia were generally younger, nulliparous with lower BMIs. 67% (47/70) had their first seizure at home, 36% (25/70) had recurrent seizures and 14% (10/70) received magnesium sulphate prior to having a seizure. Half (51%; 36/70) presented for antenatal care before 20 weeks of gestation. A blood pressure measurement before the seizure, on the same day, was available in 27% (19/70). Women with pulmonary oedema were generally older, more likely to cohabitate with a partner and had a higher caesarean section rate. In this group 82% (31/38) presented for antenatal care before 20 weeks. The mean gestational age at delivery across all groups was preterm.

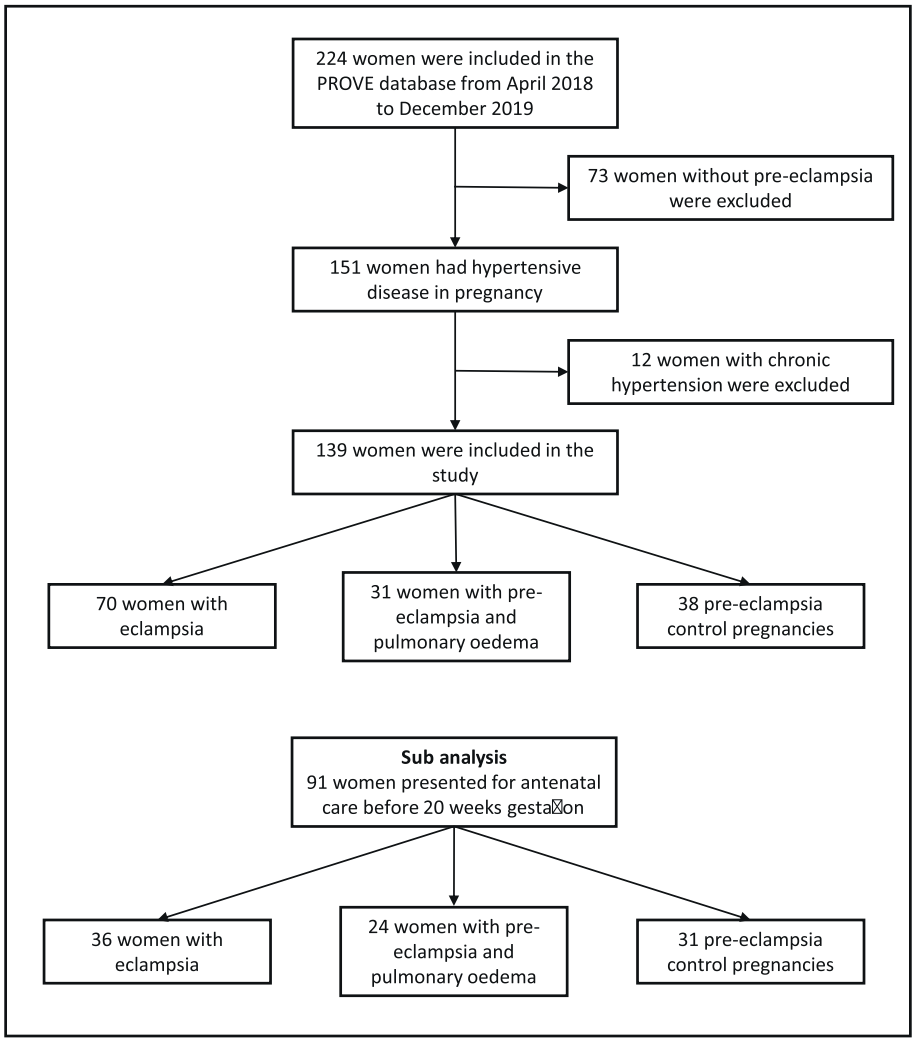

Fig. 1. Flowchart of the included population.

Table 1a
Maternal characteristics and obstetric history.

	Eclampsia (n = 36)	Pulmonary oedema (n = 24)	Pre-eclampsia controls (n = 31)
Maternal age, years (SD)	21.3 (5)	27.9 (7)	24.5 (5)
Nulliparity (%)	31 (86)	8 (33)	19 (61)
Marital status (%)			
Cohabitating	36 (51)	21 (70)	17 (45)
Single	34 (49)	9 (30)	21 (55)
Living conditions (%)			
House or apartment	19 (53)	11 (46)	19 (61)
Informal settlement	17 (47)	13 (54)	12 (39)
Body mass index (SD)	24 (4)	32 (10)	32 (5)
HIV positive (%)	2 (6)	6 (25)	6 (20)
Smoker (%)	8 (22)	3 (13)	0
Alcohol use (%)	5 (14)	0	0
Metamphetamine use (%)	1 (3)	0	0
Diabetes (%)	0	1 (4)	0
GA at delivery, weeks (SD)	33.8 (5)	32 (5)	34 (4)
Mode of delivery (%)			
Vaginal delivery	12 (33)	7 (30)	10 (32)
Emergency CS	24 (67)	16 (70)	21 (68)

Table 1b
Maternal characteristics and obstetric history of those who presented for antenatal care before 20 weeks of gestation.

	Eclampsia (n = 36)	Pulmonary oedema (n = 24)	Pre-eclampsia controls (n = 31)
Maternal age, years (SD)	21.3 (5)	27.9 (7)	24.5 (5)
Nulliparity (%)	31 (86)	8 (33)	19 (61)
Marital status (%)			
Cohabitating	36 (51)	21 (70)	17 (45)
Single	34 (49)	9 (30)	21 (55)
Living conditions (%)			
House or apartment	19 (53)	11 (46)	19 (61)
Informal settlement	17 (47)	13 (54)	12 (39)
Body mass index (SD)	24 (4)	32 (10)	32 (5)
HIV positive (%)	2 (6)	6 (25)	6 (20)
Smoking (%)	8 (22)	3 (13)	0
Alcohol use (%)	5 (14)	0	0
Metamphetamine use (%)	1 (3)	0	0
Diabetes (%)	0	1 (4)	0
GA at delivery, weeks (SD)	33.8 (5)	32 (5)	34 (4)
Mode of delivery (%)			
Vaginal delivery	12 (33)	7 (30)	10 (32)
Emergency CS	24 (67)	16 (70)	21 (68)

Abbreviations: SD = standard deviation; GA = gestational age; CS = caesarean section.

3.2. Blood pressure changes

Systolic and diastolic blood pressure measurements at inclusion are presented in Table 2. After the diagnosis of pre-eclampsia, women with pulmonary oedema experienced higher systolic blood pressures than pre-eclampsia controls (mean systolic blood pressure [sBP] 180 mmHg (95% CI 169–190) vs 163 mmHg (95% CI 157–168), $p < 0.001$). Women with eclampsia demonstrated higher diastolic blood pressures at the time of diagnosis of eclampsia when compared to pre-eclampsia controls (mean diastolic blood pressure [dBP] 108 mmHg, (95% CI 102–114) vs 99 mm Hg (95% CI 93–104)). When adjusting for maternal age and body mass index as confounders, the results remained similar. The results remained consistent when only those who presented for antenatal care before 20 weeks of gestation were included (Table 3b).

In a sub analysis of women who presented for antenatal care before 20 weeks of gestation, there was no significant difference in systolic or diastolic blood pressures at presentation for antenatal care in early pregnancy between the three groups (Table 3a). Changes in systolic and diastolic blood pressure from booking to inclusion are shown in Table 3c. Women with pulmonary oedema demonstrated a larger increase in systolic blood pressure from booking to inclusion when compared to pre-eclampsia controls (ΔsBP 55 mmHg (95% CI 44–66) vs 41 mmHg (95% CI 35–48), $p < 0.05$). Women with eclampsia demonstrated a larger increase in diastolic blood pressure values from first presentation for antenatal care to pre-eclampsia diagnosis when compared to pre-eclampsia controls (ΔdBP 41 mmHg (95% CI 34–37) vs 28 mmHg (95% CI 23–34), $p < 0.01$). After adjusting for age and BMI as confounders the results remained similar. The delta values were mainly driven by the blood pressure at inclusion, after diagnosis of pre-eclampsia. When assessing blood pressure measurements before and after eclampsia there was no significant difference between these values (sBP 167 mmHg and dBP 104 mmHg before seizures vs sBP 156 mm Hg and dBP 92 mmHg after seizures).

4. Discussion

After the diagnosis of pre-eclampsia, women with pulmonary oedema experienced significantly higher systolic blood pressure measurements, whilst women with eclampsia demonstrated higher diastolic blood pressure measurements when compared with pre-eclampsia controls. In a sub analysis of those who presented for antenatal care before 20 weeks of gestation, there was no significant differences in diastolic and systolic blood pressure between the three groups at presentation for care, but women with pulmonary oedema experienced a larger increase in systolic blood pressure from early pregnancy to diagnosis of pre-eclampsia and those with eclampsia experienced a larger increase in diastolic blood pressure values from early pregnancy to diagnosis of pre-eclampsia. These delta values were mainly driven by the absolute values at inclusion in the study, after diagnosis. Therefore, results from this study do not support the use of blood pressure levels in early pregnancy or blood pressure trends during pregnancy as predictors of eclampsia or pulmonary oedema in women diagnosed with pre-eclampsia.

To our knowledge there are no other studies assessing blood pressure and blood pressure trends in women with pre-eclampsia and its most severe complications from first presentation for antenatal care to diagnosis.

A systematic review performed by our group assessing predictors for eclampsia showed the most commonly reported predictors were headache, visual disturbances and epigastric pain. Unfortunately, these symptoms all demonstrated poor predictive ability for eclampsia. Absolute values of systolic and/or diastolic blood pressure at diagnosis of pre-eclampsia were reported as risk factors for eclampsia in three studies ranging from very low to high predictive ability. There was considerable heterogeneity between studies and no data of blood pressure measurements from early pregnancy were reported [10]. Among all studies reporting on blood pressure measurements, increased diastolic blood pressure >110 mm Hg at diagnosis or pre-eclampsia had the greatest diagnostic accuracy with a sensitivity of 86% at a specificity of 86% for eclampsia but this data was derived from one case-control study, limiting the quality of evidence. Our data supports this finding and diastolic blood pressure could potentially be a valuable contributor when assessing the risk of eclampsia in women with pre-eclampsia.

In agreement with other studies [7,10,11], women with eclampsia did not demonstrate increased systolic blood pressure compared to pre-eclampsia without end-organ complications. Why certain women develop eclampsia is not clear. A common theory is loss of cerebral autoregulation and forced dilatation of cerebral vessels due to a high systolic blood pressure, mainly based on animal studies [16]. The finding that women with eclampsia do not demonstrate increased systolic blood pressure compared to women with pre-eclampsia without end-organ complications, and that eclampsia often occurs at lower systolic blood pressures than those required for cerebral autoregulatory breakthrough, argues against this. An impaired dynamic cerebral autoregulation, which is not dependant on absolute blood pressure values but rather delays in regulation of cerebral blood flow in response to fluctuations in systemic blood pressure, may better explain the underlying pathophysiology. Whether dynamic cerebral autoregulation is more severely affected by increased diastolic blood pressure is not known. Our results, in combination with previous data regarding increased diastolic blood pressure in eclampsia [2], may be of importance regarding the underlying pathophysiology and should be studied in more detail.

Our finding that women with pulmonary oedema demonstrated increased systolic blood pressure measurements compared to women with pre-eclampsia without end-organ complication is not surprising. A mechanism behind pulmonary oedema in pre-eclampsia is increased afterload with elevated systolic blood pressure, due to vasoconstriction. Thus further increase in systolic blood pressure in pre-eclampsia could place these women at higher risk of developing pulmonary oedema. Data have shown that mean arterial blood pressure is a risk factor for pulmonary oedema in pre-eclampsia [17]. Other studies have shown that systolic blood pressure is a risk factor for composite adverse outcome in pre-eclampsia but not specifically for pulmonary oedema [18,19]. To our knowledge, this is the first study to demonstrate that

Table 2
Results of blood pressure at inclusion in the study in women with eclampsia, pulmonary oedema and pre-eclampsia controls irrespective of gestational week at booking.

	n=	dBP (95% CI) Mean dBP	*P-value*	n=	dBP (95 % CI) EMM	*P-value*	n=	sBP (95% CI) Mean sBP	*P-value*	n=	sBP (95 % CI) EMM	*P-value*
			<0.05			0.145			<0.01			0.058
Eclampsia	70	108 (103, 113)	<0.05	53	106 (101, 111)	<0.05	70	171 (165, 177)	0.084	53	169 (163, 175)	0.134
Pulmonary oedema	31	105 (99, 112)	0.156	29	103 (96, 110)	0.260	31	180 (171, 189)	<0.001	29	176 (168, 184)	<0.05
Pre-eclampsia control	38	99 (95, 102)	ref	37	99 (93, 104)	ref	38	163 (158, 168)	ref	37	163 (156, 170)	ref

Values are presented as means and estimated marginal means with 95% confidence intervals (CI). Results retrieved from one-way ANOVA and multi-way ANOVA with maternal age and maternal body mass index as continuous covariates and group as fixed effect for EMM. Parameter estimates with robust standard error to adjust for differences in variance. Pairwise comparisons versus normotensive with Bonferroni correction.
Abbreviations: EMM = Estimated Marginal Means.

Table 3a
Results of blood pressure at booking in women with eclampsia, pulmonary oedema and pre-eclampsia controls. Only women presenting before 20 weeks of gestation.

	n=	dBP (95% CI) Mean dBP	*P-value*	n=	dBP (95 % CI) EMM	*P-value*	sBP (95% CI) Mean sBP	*P-value*	sBP (95 % CI) EMM	*P-value*
			0.223			0.304		0.056		0.118
Eclampsia	35	68 (64, 72)	0.578	34	68 (65, 72)	0.242	117 (114, 121)	0.262	118 (114, 122)	0.289
Pulmonary edema	24	72 (69, 76)	0.714	23	72 (68, 77)	0.658	124 (119, 130)	>0.99	125 (120, 130)	0.269
Pre-eclampsia control	31	71 (67, 74)	ref	30	71 (68, 75)	ref	121 (117, 125)	ref	121 (117, 125)	ref

Table 3b
Results of blood pressure at inclusion in the study in women with eclampsia, pulmonary oedema and pre-eclampsia controls. Only women presenting before 20 weeks of pregnancy.

	n=	dBP (95% CI) Mean ΔdBP	*P-value*	n=	dBP (95 % CI) EMM	*P-value*	sBP (95% CI) Mean ΔdBP	*P-value*	sBP (95 % CI) EMM	*P-value*
						<0.05				0.068
Eclampsia	35	108 (102, 114)	<0.01	34	110 (104, 115)	<0.01	167 (159, 175)	0.810	168 (161, 176)	0.200
Pulmonary oedema	24	105 (96, 113)	0.390	23	102 (95, 108)	0.529	180 (169, 190)	<0.01	176 (166, 185)	<0.05
Pre-eclampsia control	31	99 (95, 102)	ref	30	99 (93, 104)	ref	163 (157, 168)	ref	162 (154, 169)	ref

Table 3c
Results of blood pressure changes from presentation for antenatal care to inclusion in the study in women with eclampsia, pulmonary oedema and pre-eclampsia controls. Only women presenting before 20 weeks of gestation.

	n=	ΔdBP (95% CI) Mean ΔdBP	*P-value*	n=	ΔdBP (95 % CI) EMM	*P-value*	ΔsBP (95% CI) Mean ΔdBP	*P-value*	ΔsBP (95 % CI) EMM	*P-value*
			<0.05			<0.05		0.084		0.080
Eclampsia	35	41 (34, 47)	<0.01	34	39 (33, 45)	<0.01	49 (41, 57)	0.158	48 (40, 56)	0.181
Pulmonary edema	24	32 (23, 41)	0.892	23	32 (25, 39)	0.532	55 (44, 66)	<0.05	54 (45, 64)	<0.05
Pre-eclampsia control	31	28 (23, 34)	ref	30	28 (23, 34)	ref	41 (35, 48)	ref	41 (34, 49)	ref

Values are presented as means and estimated marginal means with 95% confidence intervals (CI). Results retrieved from one-way ANOVA and multi-way ANOVA with maternal age, maternal body mass index as continuous covariates and group as fixed effect for EMM. Parameter estimates with robust standard error to adjust for differences in variance.
Pairwise comparisons versus normotensive with Bonferroni correction.
Abbreviations: EMM = Estimated Marginal Mean.

women with pulmonary oedema present with an increased systolic, but not diastolic blood pressure compared to women with pre-eclampsia without organ complications. If this is true also before onset of pulmonary oedema is not yet shown.

The strengths of our study include the high number cases of eclampsia and pulmonary oedema seen at our referral hospital. In addition, several women with severe hypertension were included in all three groups. The PROVE database includes detailed clinical information and copies of clinical notes enabling accurate data retrieval of blood pressure recordings. Limitations include patient and healthcare related factors. A large proportion of women included only presented for antenatal care after 20 weeks of gestation. Many women did not present to a healthcare facility before experiencing eclampsia, although blood pressure values before and after the onset of seizures appeared similar. For women with pulmonary oedema, only blood pressure levels after diagnosis of pulmonary oedema were available. Other limitations are that the standard of measuring blood pressure at the different health care levels may have varied and not all used devices validated for pregnancy. We also did not adjust for pre-hypertension and anti-hypertensive treatment.

Identifying women who have had an increase in systolic or diastolic pressure at diagnosis of pre-eclampsia may help triage those who would need magnesium sulphate to prevent eclampsia and those in whom intensive blood pressure control is needed to prevent pulmonary oedema. Identifying women at higher risk for these complications may enable limited resources to be used more efficiently.

5. Conclusion

Our results show that in this population, blood pressure measurements in early pregnancy were not risk factors for the development of pulmonary oedema or eclampsia. Thus they do not seem useful when evaluating a woman presenting with pre-eclampsia for the risk of these organ complications. At the time of diagnosing pre-eclampsia, an increased diastolic blood pressure measurement may be a risk factor for the development of eclampsia and an increased systolic blood pressure measurement may be a risk factor for the development of pulmonary oedema. Further research is needed to confirm these findings.

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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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