Effect of pregnancy prolongation in early-onset pre-eclampsia on postpartum maternal cardiovascular, renal and metabolic function in primiparous women: an observational study

EG Mulder, a C Ghossein-Doha, b JRW Crutsen, a SMJ Van Kuijk, c B Thilaganathan, d MEA Spaanderman a

Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, the Netherlands b Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands c Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands d St George’s University of London, Molecular and Clinical Sciences Research Institute, St George’s University Hospitals NHS Foundation Trust, London, UK

Correspondence: EG Mulder, Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, PO Box 616, 6200 MD Maastricht, the Netherlands. Email: eva.mulder@mumc.nl.

Accepted 19 July 2020.

Objective To evaluate the association between deferred delivery in early-onset pre-eclampsia and offspring outcome and maternal cardiovascular, renal and metabolic function in the postpartum period.

Design Observational study.

Setting Tertiary referral hospital.

Population Nulliparous women diagnosed with pre-eclampsia before 34 weeks’ gestation who participated in a routine postpartum cardiovascular risk assessment programme. Women with hypertension, diabetes mellitus or renal disease prior to pregnancy were excluded.

Methods Regression analyses were performed to assess the association between pregnancy prolongation and outcome measures.

Main outcome measures Offspring outcome and prevalence of deviant maternal cardiovascular, renal and metabolic function.

Results The study population included 564 women with a median pregnancy prolongation of 10 days (interquartile range [IQR] 4–18) who were assessed at on average 8 months (IQR 6–12) postpartum. Pregnancy prolongation after diagnosis resulted in a decrease in infant mortality (adjusted odd ratio [aOR] 0.907, 95% CI 0.852–0.965 per day prolongation). This improvement in offspring outcome was associated with an elevated risk of moderately increased albuminuria (aOR 1.025, 95% CI 1.006–1.045 per day prolongation), but not with aberrant cardiac geometry, cardiac systolic or diastolic dysfunction, persistent hypertension or metabolic syndrome.

Conclusion Pregnancy prolongation in early-onset pre-eclampsia is associated with improved offspring outcome and survival. These effects do not appear to be deleterious to short-term maternal cardiovascular and metabolic function but are associated with a modest increase in risk of residual albuminuria.

Keywords Albuminuria, cardiovascular health, deferred delivery, early-onset pre-eclampsia, hypertension, metabolic syndrome.

Tweetable abstract Pregnancy prolongation in pre-eclampsia has only a limited effect on postpartum maternal cardiovascular function.

Please cite this paper as: Mulder EG, Ghossein-Doha C, Crutsen JRW, Van Kuijk SMJ, Thilaganathan B, Spaanderman MEA. Effect of pregnancy prolongation in early-onset pre-eclampsia on postpartum maternal cardiovascular, renal and metabolic function in primiparous women: an observational study. BJOG 2020; https://doi.org/10.1111/1471-0528.16435.

Introduction

Pre-eclampsia, a gestational hypertensive disorder, substantially increases maternal and offspring morbidity and mortality. It is thought to be an endothelial disease where pathogenesis involves suboptimal placental function and cardiovascular maladaptation, mostly superimposed upon subclinical pre-existing cardiovascular and metabolic risk factors. Twenty percent of women with preterm pre-eclampsia have asymptomatic structural cardiac alterations.
or dysfunction at 1 year postpartum, and within 15 years after delivery, pre-eclampsia relates to a two- to seven-fold increased risk of coronary heart disease, stroke and related death and a four-fold increased risk of end-stage renal disease. Hypertension is prevalent in 25% of women within a few years after pregnancy and up to 20% of women meet the criteria for metabolic syndrome by that time. It is not evident whether the postpartum sequelae are a consequence of the pre-existing underlying maternal cardiovascular risk factors or due to the deleterious effects of the gestational disease itself on the maternal cardiovascular system.

Delivery is currently the only definite treatment of pre-eclampsia and scheduled delivery is clinically dependent on gestation at diagnosis, severity of maternal disease and fetal condition. This decision often presents a management dilemma because premature birth increases the risk of neonatal morbidity and mortality, whereas expectant management increases maternal jeopardy from deterioration of the pre-eclamptic condition. International guidelines generally recommend expectant management with continued, vigilant surveillance of mother and fetus, with scheduled delivery for features of severe maternal disease or signs of fetal compromise. Risk of maternal peripartum complications can be estimated by the PIERS model, which predicts adverse maternal outcomes based on a few parameters that are readily obtainable in clinical practice.

Prolongation of pregnancy by a week in women with gestational hypertensive disorders at term did not relate to increased prevalence of metabolic syndrome. However, it does seem to be associated with persistence of postpartum hypertension and with the risk of severe cardiovascular diseases, suggesting that prolonged exposure to pre-eclampsia affects remote maternal cardiovascular health. There is a real paucity of evidence on the effect of expectant management of severe, early-onset pre-eclampsia on postpartum maternal cardiovascular recovery and function. The objective of this observational study was to evaluate the association between duration of gestational disease exposure and offspring outcome and maternal cardiovascular, renal and metabolic function in primiparous women.

Material and methods

Study population

There were no patients involved, or public involvement in the design and conduct of this research. No core outcome set has been used. Informed consent related to the use of clinically acquired data for scientific analysis was obtained as is customary in the Maastricht University Medical Centre (MUMC). From 1996, postpartum assessment was offered to all women with pre-eclampsia and related complications during pregnancy. The clinical service was accessible to all women in the country and approximately 65% of women were referred by physicians from other hospitals, who mainly refer women with severe complications during their pregnancy. The assessment took place at least 4, but preferably 6 months postpartum, and women were only scheduled when not breastfeeding to measure plasma volume by the Iodine-albumin indicator dilution technique (not evaluated in this study). For our analysis, we included only women admitted to the assessment within 2 years after delivery, and with onset of pre-eclampsia before 34 weeks’ gestation, as in these women, pregnancy prolongation is assumed to benefit offspring outcome. General management of these women was according to international guidelines, recommending a temporising management plan in women without features of severe disease, and an individualised approach in women with features of severe disease. Women who presented with pre-eclampsia before 24 weeks were excluded, as expectant management was not typically offered as a standard treatment option. Women who presented with stillbirth at the time of admission were excluded, as the clinical consideration of whether to terminate pregnancy for the benefit of the fetus is no longer an issue. Multiparous women and women with pre-pregnancy hypertension, diabetes mellitus or renal disease were also excluded.

Postpartum assessment

Assessment of cardiovascular, renal and metabolic risk factors was performed in standardised conditions at a morning clinic after an overnight fast. Clinical data on obstetric history, medical history and use of medication were collected from medical files, referral letters and direct patient enquiry. Diagnosis of pre-eclampsia was taken as the gestational age at which hypertension and proteinuria were observed for the first time. Glucose, insulin, creatinine and lipid-spectrum levels were obtained from fasting blood samples. Urine was collected in the 24 hours preceding the measurements and was assayed for albumin, creatinine and total protein. Body mass index (BMI) was calculated by dividing the bodyweight in kilograms by the squared height in meters. Arterial blood pressure was measured in sitting position by a semiautomatic oscillometric device (Dinamap Vital Signs Monitor 1846; Critikon, Tampa, FL, USA) every 3 minutes. The median value of 11 measurements was reported. Transthoracic echocardiography was performed according to the American Society of Echocardiography (ASE) guidelines using a commercially available phased-array echocardiographic Doppler system (iE33 system with SS-1 or X5-1 transducers, Philips Medical Systems, Best, Netherlands). All images were acquired in left lateral position, recorded as ECG-gated digital loops and stored for off-line analysis. Using M-mode in the parasternal long-axis view, we measured left ventricular end-diastolic
(LVEDd) and end-systolic (LVESd) diameters, end-diastolic interventricular septum thickness (IVST) and the posterior (inferolateral) wall thickness (PWT). As recommended by the ASE, left ventricular mass (LVM; g) was determined using the Devereux formula: 0.8 × {1.04 × ([LVEDd + PWT + IVST]³ – [LVEDd]³) + 0.6}, indexed for body surface area.¹⁹,²⁰ Relative wall thickness (RWT) was computed using the formula: 2 × PWT/LVEDd.²⁰ Left ventricular end-diastolic (EDV) and end-systolic volumes (ESV) were determined using the Teichholz formula. Left ventricular ejection fraction (%) was calculated using the formula: ([EDV-ESD]/EDV) × 100.

Definitions
Pre-eclampsia was defined as new-onset hypertension with a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in two repeated measurements along with de novo proteinuria (≥0.3 g/24 hours or ≥2+ on dipstick analysis) after 20 weeks’ gestation. Early-onset pre-eclampsia was defined as diagnosis before 34 weeks’ gestation. HELLP syndrome was defined as haemolysis (LDH >600 U/L), elevated liver enzymes (AST and ALT >70 U/L) and low platelets (platelet count <100.10⁷/L). Small-for-gestational-age (SGA) birth was defined as neonatal birthweight below the 10th percentile of the national birthweight charts, corrected for sex of the neonate and parity.²¹ Infant mortality was defined as death within 1 year after delivery.

Cardiac systolic dysfunction was defined as an ejection fraction ≤55% and aberrant cardiac geometry was defined by left ventricular mass index >95 g/m², or RWT >0.42. Kidney function was evaluated based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria, indicating that monitoring of kidney function at least once a year is required for women with a glomerular filtration rate ≥1.73 m² or an albumin-to-creatinine ratio ≥3.0 g/mol creatinine.²²

Constituents of the metabolic syndrome were defined based on World Health Organization criteria as follows: hyperinsulinemia (fasting insulin >9.2 mU/l, fasting glucose >6.1 mmol/l, and/or homeostasis model assessment for insulin resistance [HOMA-IR] >2.2), obesity (BMI >30 kg/m²), dyslipidaemia (triglycerides ≥1.7 mmol/l or HDL-cholesterol <0.9 mmol/l), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication) and proteinuria (albuminuria >2.5 g/mol creatinine or proteinuria >0.30 g/24 h).²³ Metabolic syndrome was defined as hyperinsulinemia along with two or more of the other constituents.

Statistical analysis
Women were divided into three groups based on duration of pre-eclampsia to give a general insight in the study population characteristics. Trends in difference between groups were analysed with pregnancy prolongation in days between diagnosis and delivery as a continuous variable, and not categorically. Logistic and linear regression analysis, whenever applicable, was performed to estimate the associations between duration of pre-eclampsia and off-spring outcome, and maternal deviant cardiovascular, renal and metabolic function. Because postpartum time intervals could differ between women, we corrected for time-interval between delivery and postpartum assessment by adding time as a covariate in the multivariable regression analysis when analysing the maternal effects. In addition, adjusted odds ratios (aOR) were calculated with multivariable regression analysis. We adjusted for gestational age at delivery, maternal age, year of assessment and the presence of metabolic syndrome factors at evaluation. A two-sided P-value of 0.05 or below was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA).

Results
Between September 1996 and July 2018, 709 women with a history of early-onset pre-eclampsia were admitted to the MUMC for postpartum cardiovascular and metabolic risk assessment (Figure 1). Selecting primiparous women without pre-existing diseases resulted in 594 eligible women. Characteristics of women with onset of pre-eclampsia before 24 weeks’ gestation (n = 23) or who presented with stillbirth (n = 7) are presented in Table S1. In the analysis were 564 women whose obstetric characteristics are presented in Table 1. Median pregnancy prolongation was 10 days, gestational age at diagnosis was lower in the group of women with the longest pregnancy prolongation, and prevalence of HELLP syndrome was highest in the group with short pregnancy prolongation.

Postpartum maternal status
Regression analysis showed no differences in postpartum cardiac geometry and function, vascular function, renal function or metabolic syndrome components with pregnancy prolongation (Tables 2 and S2). The OR adjusted for the interval between delivery and postpartum assessment showed that pregnancy prolongation was associated with moderately increased postpartum albuminuria (OR 1.022, 95% CI 1.005–1.040 per day prolongation) but not with severely increased proteinuria (Table 3). After adjustments for gestational age at delivery, maternal age, year of postpartum assessment and metabolic syndrome constituents, the association with moderately increased albuminuria persisted. Pregnancy prolongation was not associated with reduced creatinine clearance, annual monitoring of kidney function advice, deviant cardiac parameters or hypertension postpartum.
Offspring outcome

There were no offspring outcomes associated with pregnancy prolongation, apart from higher absolute birthweight in women whose pregnancy was prolonged longer (Table 1). Pregnancy prolongation did not increase the risk of placental abruption, stillbirth or prevalence of SGA neonates but was associated with a significant decrease in infant mortality (OR 0.952, 95% CI 0.909–0.998) (Table S3). When adjusted for gestational age at diagnosis, concurrent HELLP syndrome and eclampsia, and year of assessment, the beneficial effect of pregnancy prolongation on infant survival persisted (aOR 0.907, 95% CI 0.852–0.965).

Discussion

Main findings

This observational study demonstrates that pregnancy prolongation in early-onset pre-eclampsia is related to improved offspring outcome and survival but is not associated with deleterious effects on maternal cardiovascular, renal and metabolic function in the postpartum period, other than an increased risk of moderately increased albuminuria.

Strengths and limitations

The strength of our study is the extensive postpartum assessment of risk factors, which enabled us to correct for cardiovascular and renal risk factors. Some limitations also need to be addressed. Firstly, detailed information on anti-hypertensive treatment, target blood pressure and other

Table 1. Obstetric characteristics of study population categorised by duration of pregnancy prolongation

| Pregnancy outcome | Total n = 564 | ≤6 days n = 186 | 7–13 days n = 173 | ≥14 days n = 205 | P-value* |
|-------------------|--------------|----------------|------------------|------------------|----------|
| Prolongation in days | 10 [4–18] | 3 [1–4] | 9 [7–11] | 21 [17–30] |          |
| GA at diagnosis | 30° [28°–32°] | 31° [29°–32°] | 30° [28°–32°] | 30° [27°–32°] | <0.001  |
| GA at delivery | 32° [29°–33°] | 31° [29°–33°] | 31° [29°–33°] | 33° [30°–35°] | <0.001  |
| HELLP syndrome | 404/564 (72%) | 134/186 (72%) | 131/173 (76%) | 139/205 (68%) | 0.017   |
| Eclampsia | 34/564 (6%) | 17/186 (9%) | 5/173 (3%) | 13/205 (6%) | 0.690   |
| Birthweight, g | 1400 [1000–1810] | 1348 [975–1677] | 1270 [875–1680] | 1620 [1165–2060] | <0.001  |
| Birthweight centile | 16 [8–30] | 18 [8–32] | 16 [8–25] | 15 [8–31] | 0.805   |
| Multifetal pregnancy | 20/564 (4%) | 7/186 (4%) | 5/173 (3%) | 8/205 (4%) | 0.936   |
| SGA birth/neonate | 179/564 (32%) | 54/186 (29%) | 55/173 (32%) | 70/205 (34%) | 0.255   |
| Placental abruption | 19/564 (3%) | 10/186 (5%) | 5/173 (3%) | 4/205 (2%) | 0.109   |
| Offspring demise | 36/564 (6%) | 15/186 (8%) | 13/173 (8%) | 8/205 (4%) | 0.036   |
| Stillbirth | 8/564 (1%) | 2/186 (1%) | 4/173 (2%) | 2/205 (1%) | 0.559   |
| Infant mortality | 28/564 (5%) | 13/186 (7%) | 9/173 (5%) | 6/205 (2%) | 0.042   |

GA, gestational age; SGA, small for gestational age.

Data are presented as median [interquartile range], or number/known outcome (percentage in group).

*P-value indicates trend based on regression analysis with pregnancy prolongation used as a continuous variable.
## Table 2. Pregnancy prolongation and postpartum maternal cardiovascular, renal and metabolic function

|                                | Total      | ≤6 days     | 7–13 days   | ≥14 days    | P-value* |
|--------------------------------|------------|-------------|-------------|-------------|----------|
|                                | n = 564    | n = 186     | n = 173     | n = 205     |          |
| Time to assessment (months)    | 8 [6–12]   | 8 [6–12]    | 7 [6–12]    | 8 [6–14]    | 0.006    |
| Maternal age (years)           | 30.4 (4.2) | 29.9 (4.0)  | 30.6 (4.1)  | 30.8 (4.5)  | 0.090    |
| Cardiac parameters             |            |             |             |             |          |
| LVM index (g/m²)               | 70 [61–79] | 69 [61–79]  | 69 [60–78]  | 71 [61–80]  | 0.916    |
| Relative wall thickness (%)    | 0.33 [0.30–0.35] | 0.33 [0.30–0.35] | 0.32 [0.30–0.35] | 0.33 [0.30–0.35] | 0.698    |
| Ejection fraction (%)          | 64 [61–67] | 64 [61–67]  | 64 [60–67]  | 64 [60–67]  | 0.861    |
| Vascular function              |            |             |             |             |          |
| Albuminuria (g/mol creatinine)| 1.0 [0.5–2.3] | 0.8 [0.4–1.9] | 1.0 [0.6–2.2] | 1.2 [0.5–2.7] | 0.643    |
| Proteinuria (g/mol creatinine)| 8.2 [6.7–10.5] | 8.0 [6.7–10.3] | 7.9 [6.4–10.3] | 8.9 [7.0–11.4] | 0.941    |
| CC (ml/min/1.73 m²)            | 106 [95–117] | 107 [97–118] | 105 [93–117] | 104 [93–115] | 0.209    |
| Renal parameters               |            |             |             |             |          |
| Proteinuria or albuminuria     | 121/544 (22%) | 31/178 (17%) | 32/168 (19%) | 58/203 (29%) | 0.061    |

cc, creatinine clearance; LVM, left ventricular mass.

Data are presented as mean (standard deviation), median [interquartile range] or number/valid measurements (percentage in group).

*P-value indicates trend based on regression analysis with pregnancy prolongation (days) used as a continuous variable.

## Table 3. Association between pregnancy prolongation after pre-eclampsia diagnosis (per day prolongation) and maternal cardiovascular, renal and metabolic function

|                                | OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
|--------------------------------|-------------|---------|----------------------|---------|
| Cardiac parameters             |             |         |                      |         |
| Left ventricular mass index >95 g/m² | 1.005 [0.956–1.056] | 0.853   | 0.987 [0.928–1.050] | 0.677   |
| Relative wall thickness >0.42 | 1.023 [0.971–1.078] | 0.398   | 1.001 [0.932–1.074] | 0.987   |
| Ejection fraction <55%         | 0.956 [0.873–1.047] | 0.333   | 0.931 [0.840–1.031] | 0.170   |
| Renal parameters               |             |         |                      |         |
| Albuminuria >2.5 g/mol creatinine* | 1.022 [1.005–1.040] | 0.011   | 1.025 [1.006–1.045] | 0.010   |
| Proteinuria >30 g/mol creatinine* | 0.998 [0.932–1.069] | 0.995   | 0.994 [0.924–1.071] | 0.994   |
| Creatinine clearance <90 ml/min/1.73 m² | 1.011 [0.993–1.029] | 0.234   | 1.001 [0.981–1.022] | 0.904   |
| Annual monitoring necessary according to KDIGO* | 1.013 [0.995–1.031] | 0.173   | 1.013 [0.993–1.034] | 0.211   |
| Metabolic syndrome*            | 1.012 [0.993–1.032] | 0.228   | 1.014 [0.993–1.036] | 0.182   |
| Hyperinsulinemia*              | 0.998 [0.984–1.012] | 0.774   | 1.005 [0.988–1.023] | 0.549   |
| Obesity*                       | 1.005 [0.989–1.022] | 0.534   | 1.008 [0.988–1.028] | 0.450   |
| Dyslipidaemia*                 | 1.003 [0.985–1.021] | 0.755   | 0.996 [0.975–1.017] | 0.702   |
| Hypertension*                  | 1.004 [0.986–1.023] | 0.653   | 1.010 [0.989–1.032] | 0.339   |
| Albuminuria or proteinuria*    | 1.021 [1.004–1.039] | 0.014   | 1.024 [1.005–1.044] | 0.015   |

KDIGO, Kidney Disease Improving Global Outcomes.

ORs are adjusted for months between delivery and postpartum assessment.
aORs are adjusted for gestational age at delivery, maternal age, year of postpartum assessment, hyperinsulinemia, hypertension, obesity, dyslipidaemia, and moderately increased albuminuria, or severely increased proteinuria.

*Not adjusted for specific metabolic syndrome component(s).
treatment goals during pregnancy is lacking. Therefore, we are not able to evaluate the effect of specific treatment on pregnancy prolongation and outcomes. In addition, as we do not have detailed information on the maternal condition that contributed to the physicians’ decision to terminate pregnancy, it could be possible that immediate scheduled birth was planned because of rapid deterioration of maternal condition. This would mitigate the association between pregnancy prolongation and maternal outcomes. On the other hand, pregnancy prolongation might be associated with more advanced maternal disease contributing to residual albuminuria postpartum. However, the decision to end pregnancy is often not based on increase or magnitude of proteinuria, as this does not affect maternal or perinatal outcome.24 Lastly, as women had to attend the postpartum evaluation, we were not able to assess maternal death as outcome of a temporising management plan. Although absolute numbers of maternal deaths are low, and most maternal deaths occur after 34 weeks of pregnancy, postponing delivery in early-onset pre-eclampsia exposes the women to increased risk of mortality.25,26

**Interpretation**

In pre-eclampsia diagnosed before 34 weeks’ gestation, immediate induction of labour increases the risk of neonatal mortality and morbidity, and pregnancy prolongation is preferred as long as maternal and fetal condition permits.27,28 In our sample, pregnancy was prolonged for 10 days, which is slightly longer than in other studies despite the relatively high incidence of HELLP syndrome.28–30 Women whose pregnancy was prolonged the longest, had earlier onset of pre-eclampsia, which probably explains the observed neonatal health gain of postponing delivery. Clinicians are more likely to take the risk of short-term maternal and fetal complications when the survival rate of the neonate is expected to be considerably improved with pregnancy prolongation.31 Deferred delivery was associated with a decreased risk of infant mortality and resulted in higher absolute birthweight, which in turn also contributes to an increased survival rate.32 The presumption that the in utero environment may be suboptimal for the growth potential of the fetus could not be substantiated by our observations, as the relative birthweight did not deteriorate with prolonged pregnancy.33,34

Prevalence of hypertension and blood pressure levels did not relate to pregnancy prolongation, nor did estimates of arterial compliance. The reason might be that clinical pre-eclampsia does not induce persistent vascular alterations, or that this contribution is minor compared with disease evolution prior to diagnosis. The changes in cardiac geometry during normotensive pregnancy generally recover in the postpartum period.35 In contrast, after preterm pre-eclampsia, about half of women show asymptomatic structurally altered cardiac geometrics consisting mainly of concentric left ventricular remodelling, even after several years.36 Concentric remodelling is known for its association with increased myocardial fibrosis, which decreases left ventricular compliance and consequently impairs diastolic function.4,36 About a quarter of women in our population had a left ventricle mass index >80 g/m², which is above the upper limit of non-pregnant reference values.37 In addition, the RWT of our women was comparable to other formerly pre-eclamptic women, being substantially higher than the postpartum RWT in women with uncomplicated pregnancies.38 There was no association between pregnancy prolongation and deviant cardiac geometric indices and prevalence of global left ventricular dysfunction. A possible explanation could be that the known association with unfavourable structural alteration in pre-eclampsia may have already occurred by the time the diagnosis was made. A meta-analysis showed that the steepest change in left ventricular remodelling occurs before 30 weeks.37 Moreover, when pre-eclampsia is diagnosed, blood pressure-lowering medication is initiated, which may temper further geometrical changes and myocardial damage.39 It is also conceivable that the time-span of estimated disease prolongation is too short to result in deleterious effects on cardiac geometry.

The median albumin-to-creatinine ratio in our population was 1.0 g/mol (0.5–2.3 g/mol), which is slightly higher than the normal range in healthy women aged between 20 and 40 years (0.7 g/mol to 0.4–1.1 g/mol).40 Pre-eclamptic women with prolonged pregnancy have a slightly higher risk of residual moderately increased albuminuria postpartum, but glomerular filtration rate and serum creatinine level were not affected. Also, pregnancy prolongation did not increase the prevalence of severely increased proteinuria, which usually resolves within weeks to months postpartum.15 These observations suggest a higher risk on moderate endothelial dysfunction when a policy of pregnancy prolongation is pursued. It is uncertain whether residual albuminuria reflects incomplete recovery from permanent damage incurred during pregnancy or undetected pre-existing endothelial dysfunction predisposing to pre-eclampsia and postpartum diagnosis of albuminuria.51,52 Pre-eclampsia is associated with an upregulation of placental sFlt-1, which scavenges vascular endothelial growth factor (VEGF). Reduction of VEGF in mice results in proteinuria and glomerular endotheliosis, resembling pre-eclampsia.43 VEGF is a signal protein produced by podocytes with autocrine function to support cell survival, and paracrine function on the glomerular endothelial cells.44 The degree of damaged podocytes correlates with the intensity of proteinuria, and depletion up to 20% results in a transient increase in proteinuria, with preserved creatinine clearance.45 Proteinuria itself is potentially harmful to the proximal tubule and podocytes, as proteins in the glomerular
ultrafiltrate activate inflammation and fibrosis, and the presence of proteins impairs podocyte regeneration.46,47

Our results emphasise the importance of monitoring the presence of moderately increased albuminuria in women with early-onset pre-eclampsia, especially in women whose pregnancy is prolonged by several weeks. To date, no specific interventions to improve long-term outcomes are evidenced, but adequate blood pressure control in hypertension, lifestyle and exercise advice might lower albuminuria in screen-positive women.48,49

Postpartum metabolic syndrome was observed in 15% of women in our population, compared with a prevalence of 5% in Dutch women of similar age.50 Prevalence was not related to duration of preeclampsia—nor were the individual components of the metabolic syndrome other than albuminuria. Similar results were found in women with gestational hypertensive disorders at term whose induction of labour was postponed for a week compared with immediate delivery.14 As hypertensive complications during pregnancy are associated with exaggerated metabolic changes prior to overt clinical disease, it might be unlikely that duration of pre-eclampsia affects the development of metabolic syndrome postpartum.51–53 These findings support the concept of Romundstad et al. who suggested that postpartum development of metabolic syndrome is attributable to shared pre-pregnancy risk factors rather than a direct influence of gestational hypertensive disorders.7

Conclusion

Prolongation of pregnancy in early-onset pre-eclampsia with consideration of individual context at the discretion of the attending obstetrician relates to reduced infant mortality. Moreover, it is associated with a raised prevalence of moderately increased albuminuria but does not seem to have an adverse effect on cardiovascular function or metabolic status. It is unknown how these findings translate to long-term cardiovascular morbidity. Our findings should also be evaluated in a setting with detailed information on disease severity at presentation and peripartum management.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

EM, CG, BT and MS were involved in the design and initiation of the study. EM, CG, MS acquired ethical approval. EM and JC had full access to the data in the study and take responsibility for the integrity of the data. SvK provided statistical expertise. All authors interpreted the data. EM and JC wrote the first draft of this protocol, and all authors critically reviewed and contributed to adjustments and approved the final version of this manuscript.

Details of ethics approval

The medical ethical committee of the Maastricht University Medical Centre approved the study protocol (date of approval last study amendment: 12 August 2019, reference number: MEC azM/UM 14-4-118).

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Chahinda Ghossein-Doha was personally supported by a Mosaic Fellowship for young talented researchers from the Netherlands Organization for Scientific Research (NWO). Basky Thilanganathan is partly funded by ‘European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 765274’.

Acknowledgements

Not applicable.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of women with pre-eclampsia before gestational age of 24 weeks or who presented with stillbirth admitted to the postpartum within 2 years after delivery.

Table S2. Pregnancy prolongation and postpartum maternal cardiovascular, renal and metabolic function.

Table S3. Association between pregnancy prolongation after pre-eclampsia diagnosis (days) and offspring outcome.

References

1 Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Pre-pregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ 2007;335:978.
2 Burton GJ, Jauniaux E. Placental oxidative stress: from miscarriage to pre-eclampsia. J Soc Gynecol Investig 2004;11:342–52.
3 Bosio PM, McKenna PJ, Conroy R, O’Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstet Gynecol 1999;94:978–84.
4 Melchiore K, Sutherland GR, Liberati M, Thilanganathan B. Pre-eclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension 2011;58:709–15.
5 Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Pre-eclampsia and future cardiovascular health. a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2017;10:e003497.
6 Hooischuur MC, Ghoessein-Doha C, Al-Nasiry S, Spaanderman ME. Maternal metabolic syndrome, pre-eclampsia, and small for gestational age infancy. Am J Obstet Gynecol 2015;213:370.e1–e7.
7 Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation 2010;122:579–84.
8 Cho GJ, Jung US, Sim JY, Lee YJ, Bae NY, Choi HJ, et al. Is pre-eclampsia itself a risk factor for the development of metabolic syndrome after delivery? Obstet Gynecol Sci 2019;62:233–41.
9 Vikse BE. Pre-eclampsia and the risk of kidney disease. Lancet 2013;382:104–6.
10 Wang Y, Hao M, Sampson S, Xia J. Elective delivery versus expectant management for pre-eclampsia: a meta-analysis of RCTs. Arch Gynecol Obstet 2017;295:607–22.
11 National Institute for Health and Clinical Excellence Hypertension in pregnancy: the management of hypertensive disorders of pregnancy NICE clinical guideline 107, August 2010. [cited; Available from: https://www.nice.org.uk/guidance/cg107].
12 ACOG Practice Bulletin No. 202: Gestational hypertension and pre-eclampsia. Obstet Gynecol 2019;133:e1–e25.
13 Ukah UV, Payne B, Hutcione JA, Ansermino JM, Ganzewoert W, Thangaratnam S, et al. Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Pre-eclampsia. Hypertension 2018;71:659–65.
14 Hermes W, Koopmans CM, van Pampus MG, Franx A, Bloemenkamp KW, van der Post J, et al. Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: do women’s postpartum cardiovascular risk factors differ between the two strategies? Eur J Obstet Gynecol Reprod Biol 2013;171:30–4.
15 Berks D, Steegers EA, Molas M, Visser W. Resolution of hypertension and proteinuria after pre-eclampsia. Obstet Gynecol 2009;114:1307–14.
16 Rosenblum JL, Lewkowitz AK, Lindley KJ, Nelson DM, Macones GA, Cahill AG, et al. Expectant management of hypertensive disorders of pregnancy and future cardiovascular morbidity. Obstet Gynecol 2020;135:27–35.
17 Gaugler-Senden IP, Huisgoon AG, Visser W, Steegers EA, de Groot CJ. Maternal and perinatal outcome of pre-eclampsia with an onset before 24 weeks’ gestation. Audit in a tertiary referral center. Eur J Obstet Gynecol Reprod Biol 2006;128:216–21.
18 Mitchell C, Rahko PS, Blauvelt LA, Canaday B, Finsuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the american society of echocardiography: J Am Soc Echocardiogr 2019;32(1):1–64.
19 Devereux RB, Alonso DR, Lutas EM, Gottlieb GS, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
20 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
21 Kloosterman GJ. Intratrauterine growth and intrauterine growth curves. Ned Tijdschr Verloskd Gynaecol 1969;69:349–65.
22 Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes clinical practice guideline. Ann Intern Med 2013;158:825–30.
23 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. Diabetic Med 1998;15:539–53.
24 Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol 2010;115(2 Pt 1):365–75.
25 Schutte JM, Schuitemaker NW, van Roosmalen J, Steegers EA. Dutch Maternal Mortality C. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. BJOG 2008;115:732–6.
26 Ackerman CM, Platner MH, Spatz ES, Illuzzi JL, Xu X, Campbell KH, et al. Severe cardiovascular morbidity in women with hypertensive diseases during delivery hospitalization. Am J Obstet Gynecol 2019;220:582.e1–e11.
27 Magee LA, Yong PJ, Espinosa V, Cote AM, Chen I, von Dadelszen P. Expectant management of severe pre-eclampsia remote from term: a structured systematic review. Hypertens Pregnancy 2009;28:312–47.
28 Ganzewoert W, Sibai BM. Temporising versus interventionist management (preterm and at term). Best Pract Res Clin Obstet Gynaecol 2011;25:463–76.
29 Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks’ gestation. Cochrane Database Syst Rev 2018(10):CD003106.
30 Abramovici D, Friedman SA, Mercer BM, Audibert F, Kao L, Sibai BM. Neonatal outcome in severe pre-eclampsia at 24 to 36 weeks’ gestation: does the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome matter? Am J Obstet Gynecol 1999;180(1 Pt 1):221–5.
31 Haddad B, Deis S, Goffinet F, Paniel BJ, Cabrol D, Sibai BM. Maternal and perinatal outcomes during expectant management of 239 severe pre-eclamptic women between 24 and 33 weeks’ gestation. Am J Obstet Gynecol 2004;190:1590–5;discussion 5–7.
32 Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. BMJ 1999;319:1093–7.
33 Wiltin AG, Saade GR, Mattar F, Sibai BM. Predictors of neonatal outcome in women with severe pre-eclampsia or eclampsia between 24 and 33 weeks’ gestation. Am J Obstet Gynecol 2000;182:607–11.
34 Mateus J, Newman RB, Zhang C, Pugh SJ, Greavel J, Kim S, et al. Fetal growth patterns in pregnancy-associated hypertensive disorders: NICHD Fetal Growth Studies. Am J Obstet Gynecol 2019;221:635.e1–e16.
35 Melchiore K, Sharma R, Khallal A, Thilaganathan B. Maternal cardiovascular function in normal pregnancy: evidence of maladaptation to chronic volume overload. Hypertension 2016;67:754–62.
36 Orabona R, Sciatti E, Vizzardi E, Bonadei I, Prefumo F, Valcamonica A, et al. Ultrasound evaluation of left ventricular and aortic fibrosis after pre-eclampsia. Ultrasound Obstet Gynecol 2018;52:648–53.
37 de Haas S, Ghoessein-Doha C, Geerts L, van Kuijk SM, van Drongelen J, Spaanderman ME. Cardiac remodeling during normotensive and hypertensive complicated pregnancies: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2017;50:683–96.
38 Venables H, Lo Presti D, Gagliardi G, Tiralongo GM, Pisani I, Novelli GP, et al. Persistent maternal cardiac dysfunction after pre-eclampsia identifies patients at risk for recurrent pre-eclampsia. Hypertension 2016;67:748–53.
39 Fagard RH, Celis H, Tijdsschr Gynaecol 1969;69:349–65.
40 Mulder et al.
40 Chong J, Fotheringham J, Tomson C, Ellam T. Renal albumin excretion in healthy young adults and its association with mortality risk in the US population. Nephrol Dial Transplant 2018;35:458–64.

41 Hladunewich MA, Myers BD, Derby GC, Blouch KL, Druzin ML, Deen WM, et al. Course of pre-eclamptic glomerular injury after delivery. Am J Physiol Renal Physiol 2008;294:F614–F620.

42 Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. J Am Soc Nephrol 2006;17:2106–11.

43 Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. J Clin Invest 2003;111:707–16.

44 Foster RR, Hole R, Anderson K, Satchell SC, Coward RJ, Mathieson PW, et al. Functional evidence that vascular endothelial growth factor may act as an autocrine factor on human podocytes. Am J Physiol Renal Physiol 2003;284:F1263–F1273.

45 Wharram BL, Goyal M, Wiggins JE, Sanden SK, Hussain S, Filipiak WE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. J Am Soc Nephrol 2005;16:2941–52.

46 Erkan E. Proteinuria and progression of glomerular diseases. Pediatr Nephrol 2013;28:1049–58.

47 Peired A, Angelotti ML, Ronconi E, la Marca G, Mazzinghi B, Sisti A, et al. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. J Am Soc Nephrol 2013;24:1756–68.

48 Scholten RR, Hopman MT, Lotgering FK, Spaanderman ME. Aerobic exercise training in formerly pre-eclamptic women: effects on venous reserve. Hypertension 2015;66:1058–65.

49 Parati G, Ochoa JE, Bilo G. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. Curr Hypertens Rep 2012;14:421–31.

50 Bos MB, de Vries JH, Wolfenbuttel BH, Verhagen H, Hillege JL, Feikens EJ. [The prevalence of the metabolic syndrome in the Netherlands: increased risk of cardiovascular diseases and diabetes mellitus type 2 in one quarter of persons under 60]. Ned. Tijdschr Geneeskd 2007;151:2382–8.

51 Solomon CG, Graves SW, Greene MF, Seely EW. Glucose intolerance as a predictor of hypertension in pregnancy. Hypertension 1994;23(Suppl 1):717–21.

52 Wiznitzer A, Mayer A, Novack V, Sheiner E, Gilutz H, Malhotra A, et al. Association of lipid levels during gestation with pre-eclampsia and gestational diabetes mellitus: a population-based study. Am J Obstet Gynecol. 2009;201:482.e1–e8.

53 Adank MC, Benschop L, Peterbroers KR, Smak Gregoor AM, Kors AW, Mulder MT, et al. Is maternal lipid profile in early pregnancy associated with pregnancy complications and blood pressure in pregnancy and long term postpartum? Am J Obstet Gynecol 2019;221:150.e1–e13.