Unique Blood Pressure Characteristics in Mother and Offspring After Early Onset Preeclampsia

Merzaka Lazdam, Arancha de la Horra, Jonathan Diesch, Yvonne Kenworthy, Esther Davis, Adam J. Lewandowski, Cezary Szmigielski, Angela Shore, Lucy Mackillop, Rajesh Kharbanda, Nicholas Alp, Christopher Redman, Brenda Kelly, Paul Leeson

Abstract—Risk of hypertension in mother and offspring after preeclampsia is greater if preeclampsia develops early in pregnancy. We investigated whether those who develop early onset disease have unique adverse blood pressure characteristics. One hundred forty women were studied 6 to 13 years either after a pregnancy complicated by preeclampsia (45 women with early onset preeclampsia before 34 weeks gestation and 45 women with late-onset preeclampsia) or after a normotensive pregnancy (50 women). Forty-seven offspring from these pregnancies also participated. Data on maternal antenatal and postnatal blood pressures were extracted from maternity records and related to peripheral, central, and ambulatory blood pressure measurements in later life. Compared with late-onset preeclampsia, early onset preeclampsia was associated with higher diastolic blood pressure 6 weeks postnatally (86.25±13.46 versus 75.00±5.00 mm Hg, \(P<0.05\)), a greater increase in blood pressure relative to booking blood pressure over the subsequent 6 to 13 years, and higher nocturnal systolic and diastolic blood pressures in later life (\(111.07±13.18\) versus \(101.13±11.50\) mm Hg, \(P=0.04\), and \(67.00±7.25\) versus \(58.60±5.79\) mm Hg, \(P=0.002\)). Furthermore, at age 6 to 13 years their offspring had higher systolic blood pressure compared with those born to late-onset preeclampsia (96.27±7.30 versus 88.39±7.57 mm Hg, \(P=0.005\)). Mothers who developed early onset preeclampsia, and the offspring of that pregnancy display specific adverse blood pressure characteristics later in life. These are not evident in mothers and offspring after late-onset preeclampsia or normotensive pregnancy. (Hypertension. 2012;60:1338-1345.) ● Online Data Supplement

Key Words: preeclampsia ■ blood pressure ■ ambulatory blood pressure ■ lipids ■ insulin resistance ■ mother ■ child ■ offspring

Preeclampsia is a multisystem condition that complicates 2% to 8% of all pregnancies. Although hypertension and proteinuria that define preeclampsia resolve in the majority of mothers within 6 months of delivery, affected women continue to have higher ambulatory and office blood pressures (BPs) and a significantly greater risk of cardiovascular diseases, in particular, hypertension, in later life. The risk of these long-term sequelae is greatest in early onset preeclampsia diagnosed before 34 weeks gestation. This early onset disease also has distinct cardiac and vascular characteristics during pregnancy, which include impaired uteroplacental blood flow, increased peripheral vascular resistance, and reduced cardiac output. These features are not commonly observed when preeclampsia develops later in pregnancy, and this finding has led to the concept that women who develop early onset preeclampsia may have a distinct disease entity. Interestingly, mothers who develop preeclampsia before 34 weeks of gestation are more likely to have a family history of preeclampsia and to have recurrent disease in subsequent pregnancies. These observations raise the possibility that mothers develop early onset disease because they have underlying physiological or biological differences that persist beyond pregnancy and transfer between generations. We recruited a large cohort of women 10 years after pregnancy to determine whether women predisposed to early onset preeclampsia have distinct BP behavior remote from pregnancy. We then studied their offspring to determine whether early onset disease was associated with unique BP differences in the next generation.

Methods

Study Design

We identified all women discharged from the Oxford Maternity Unit between 1998 and 2003, with an International Classification of Diseases, 10th Revision, preeclampsia coding. To ensure that only women with International Society for the Study of Hypertension in Pregnancy criteria for preeclampsia were studied, maternity records of all women were extracted from the Oxford Maternity Unit between 1998 and 2003, with an International Classification of Diseases, 10th Revision, preeclampsia coding. To ensure that only women with International Society for the Study of Hypertension in Pregnancy criteria for preeclampsia were studied, maternity records

Received May 7, 2012; first decision May 31, 2012; revision accepted August 28, 2012.
From the Oxford Cardiovascular Clinical Research Facility, Department of Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom (M.L., A.d.l.H., J.D., Y.K., E.D., A.J.L., R.K., N.A., P.L.); Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom (A.d.l.H., Y.K., I.M., C.R., B.K.); Department of Internal Medicine, Warsaw University Hospital, Warsaw, Poland (C.S.); Peninsula National Institute for Health and Research Clinical Research Facility and Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, United Kingdom (A.S.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.orglookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.198366.112.198366/DCl.

Correspondence to Paul Leeson, Oxford Cardiovascular Clinical Research Facility, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom. E-mail paul.leeson@cardiov.ox.ac.uk

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Hypertension is available at http://hyper.ahajournals.org

DOI:10.1161/HYPERTENSIONAHA.112.198366

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were independently reviewed and only those with documented evidence invited. In addition, on the basis of medical records (or information collected during participation), women with hypertension, diabetes mellitus, renal impairment, polycystic ovary syndrome, or inflammatory disease at pregnancy were excluded.

From 634 retrievable records, 428 women fulfilled International Society for the Study of Hypertension in Pregnancy criteria for preeclampsia. One hundred nineteen had preexisting disease, so 309 were invited and, of these, 90 agreed to participate. For every participant, we identified potential controls, with equivalent age and parity giving birth at the Oxford Maternity Unit in the same year. A total of 536 records were reviewed, and women were not contacted if there was evidence of raised BP or proteinuria (>1+) during any pregnancy or delivery of a small-for-gestational-age infant during the index pregnancy (birthweight <10th centile), resulting in 309 control women being invited and 50 completing the study. All enrolled women were asked if they would involve their offspring in the study. All studies were approved by the Oxfordshire Research Ethics Committee, and participants provided signed informed consent or assent in accordance with the Declaration of Helsinki.

Pregnancy Data, Demographics, Anthropometry, and Blood Samples

Mothers and offspring attended a research clinic in the morning after a 12-hour fast and were assessed by investigators blinded to maternity data in temperature-controlled rooms (22–24°C). Body size was measured at a combined digital height and weight station (Marsden), which calculated body mass index. A research midwife gathered relevant medical, family, and lifestyle factors (diet, smoking, alcohol, and exercise) by questionnaire.24 Fasting blood samples were drawn from all willing participants, centrifuged, and separated within a 30-minute period, and stored at −80°C for later analysis. Total cholesterol, high-density lipoprotein, triglycerides, glucose, and insulin levels were measured at the John Radcliffe Biochemistry Laboratory. Low-density lipoprotein was calculated by Friedewald formula and insulin resistance by homeostatic model assessment. Maternal and offspring pregnancy clinical details were obtained from maternity records including parity and birthweight.

BP Measurements

Antenatal and Postnatal BP

Antenatal BP measures were extracted from maternity records including timing of measurement during pregnancy. Measures grouped according to standardized clinical antenatal visits were booking (12.14±2.69 weeks), midpregnancy (21.36±1.34 weeks), and late antenatal visits (32.49±1.43 weeks). Further measures were recorded at delivery, which varied between groups, hospital discharge, and at 6-week postnatal check for those who had preeclampsia.

Peripheral and Central BP

During the study, 2 peripheral BP readings were obtained for participants after 15 minutes of supine rest using a calibrated oscillometric device (A&D Medical). Appropriate cuff sizes for arm circumference were used (bladder 80% of length and >40% arm width).25 Radial artery waveform was recorded by applanation tonometry of the radial pulse to generate an ascending aortic waveform and central BP derived based on a mathematical transfer function (SphygmoCor, AtCor Medical).26

Ambulatory BP

Ambulatory BP monitoring was incorporated as an additional measure during the study for mothers using an oscillometric device (TM-2430, A&D Instruments) and carried out on 47 participants (15 women with early onset, 16 late-onset preeclampsia, and 15 controls). Appropriate BP cuff was determined based on arm circumference and secured to the nondominant arm using tape. Subjects were instructed to remain still during measurements. Automated measurements were performed every 30 minutes during daytime and hourly between 11:00 pm and 7:00 am. Subjects returned a diary documenting sleep and awakening hours.

Statistical Analysis

Women and children were grouped based on whether preeclampsia had developed before 34 weeks or at 34 weeks or later based on previous definitions of early onset and late-onset disease.20 Forty-five subjects per group provided 90% power (twosided) to identify a 0.75 SD difference between groups. On the basis of reported BP distributions for women of similar age, this equated to a 4- and 12-mm Hg difference. Normality was assessed by Shapiro-Wilk test and visual assessment. Comparisons between groups were assessed by Student t test for continuous variables and χ2 for categorical data with results presented as mean (SD) or number (percentage), respectively. To study relations between BP at booking and in later life, as well as whether associations varied depending on booking BP, we used Pearson correlation and a nonlinear Lowess plot. In addition, we divided the group by booking diastolic blood pressure (DBP) tertiles and compared increases in BP relative with booking between preeclampsia type. Two-tailed P values of <0.05 were considered significant. SPSS (version 17) and GraphPad Prism version 5 were used for analysis.

Results

Study Groups and Cardiovascular Risk Factors

A total of 140 women took part, of whom 45 had early onset preeclampsia, 45 late-onset preeclampsia, and 50 uncomplicated pregnancies. Subjects were aged 28 to 50 years with a mean follow-up of 9.75 years (6–13 years) after the index pregnancy. There were no differences between responders and nonresponders in booking BP (Table S1 in the online-only Data Supplement). Forty-seven women consented to their offspring taking part, of whom 14 were controls, 15 were born to early onset preeclampsia, and 18 were to late-onset preeclampsia. There were no differences in birthweight or proportion of small-for-gestational-age offspring between participants and nonparticipants (21.3% versus 22.6%, P=0.84). Both groups of preeclamptic women were 2 cm shorter (P=0.005) than controls (Table) and tended to have higher body mass index. In addition, both groups had higher insulin, homeostatic model assessment for insulin resistance factor, and lipid abnormalities (Table). At follow-up, 6 with early onset preeclampsia had diagnosed hypertension, and 1 was on oral hypoglycemics, for diabetes mellitus.

Antenatal and Postnatal BPs in the Mother

All participants were normotensive at antenatal booking (Table S2). However, women with early onset disease had significantly higher booking BPs compared with controls with no difference in DBP between those with late-onset disease and controls (Figure 1). Consistent with time of diagnosis, systolic blood pressure (SBP) and DBP rose rapidly in the early onset disease group and were significantly higher than controls and those with late-onset disease by the middle trimester (Figure 1). In contrast, BP increased more slowly in women with late-onset preeclampsia. Interestingly, despite similar peak BP during pregnancy and at hospital discharge, BP behavior then diverged between groups (Figure 1). At 6 weeks postpartum, SBP and DBP were higher in the early onset preeclampsia group with DBPs unchanged to those at hospital discharge and significantly higher than those with late-onset preeclampsia (86.25±13.46 versus 75.00±5.00 mm Hg, P=0.04). In the late-onset group, by 6 weeks, both SBP and DBP had returned to levels seen at hospital discharge.
in those with a normotensive pregnancy (SBP 119.00 ± 10.25 versus 119.25 ± 13.27 mm Hg, \( P < 0.05 \); DBP 75.00 ± 5.50 versus 74.70 ± 7.74 mm Hg, \( P = 0.93 \)).

**Later Life Peripheral, Central, and Ambulatory BPs in the Mother**

Six to 13 years postpartum women from both preeclampsia groups had higher SBP and DBP (Table S2). These differences remained significant after excluding women with diagnosed hypertension (\( P \leq 0.05 \)). There was a graded difference in 24-hour BP measures dependent on preeclampsia type (Figure 2A). Both groups exhibited similar levels of daytime SBP and DBP compared with controls. However, only women with early onset preeclampsia had higher nocturnal BP, by \(\approx 10\) mm Hg. Both controls and those with late-onset disease had similar nocturnal levels (Figure 2B).

**Associations Between Maternal Perinatal and Later Life BPs**

We next studied relations between BPs at booking and later life. Measures positively correlated both for SBP (\( r = 0.512, P < 0.001 \)) and DBP (\( r = 0.404, P < 0.001 \)) in the cohort as a whole. However, when later BP levels were related to booking pressures in each preeclampsia group, there were distinct differences. For each booking BP level, the early onset group had higher pressures in later life compared with the normotensive pregnancy and late-onset groups. This could be demonstrated both if a nonlinear Lowess plot (Figure 3A) was used and if BP change between booking and later life was plotted stratified by booking BP tertile (Figure 3B). Mean pressures in the early onset group was always 12 to 18 mm Hg higher, irrespective of booking BP level. In controls and the late-onset group, the mean BP rise was smaller, and, indeed, in those with high booking BP, there was a relative drop.

**Offspring BP**

As expected, offspring of early onset preeclampsia were more likely to be born preterm (before 37 weeks gestation; 86.67% versus 22.22%, \( P < 0.001 \)) and small for gestational age (46.67% versus 16.67%, \( P = 0.06 \)) compared with late-onset preeclampsia. Both groups had comparable age and anthropometric measures including height, head circumference, and body mass index at study visit with no differences in metabolic and inflammatory markers between groups (Table S3). However, both peripheral and central SBP were significantly higher in offspring of early onset preeclampsia compared with those born after late-onset disease (96.27 ± 7.30 versus 88.39 ± 7.57 mm Hg, \( P = 0.005 \)) (Figure 4). Interestingly, compared with controls, mothers with early onset preeclampsia were themselves more likely to have been born to preeclamptic pregnancies (17.8% versus 2%, \( P = 0.01 \)). The incidence was not significantly higher in those with late-onset disease compared with controls (8.9% versus 2%, \( P = 0.13 \)).

**Discussion**

We demonstrate for the first time that, compared with women with late-onset preeclampsia or normotensive pregnancies, women who develop early onset preeclampsia not only have higher BP at antenatal booking and in later life but also...
have persistently higher BP 6 weeks after delivery, a greater increase in BP during the subsequent 10 years relative to booking BP, and significantly higher nocturnal BPs in later life. Furthermore, they are more likely to have been born to a pregnancy complicated by preeclampsia, and their offspring have $\approx 6$-mm Hg higher SBP by age 6 to 13 years. Therefore, early onset preeclampsia associates with distinct BP patterns in both mother and offspring.

Because the pathogenesis of cardiovascular disease and preeclampsia share biological features, it has been suggested that cardiovascular risk associated with preeclampsia and gestational hypertension is predominantly driven by prepregnancy risk factors. To understand whether early onset preeclampsia may have a unique relevance to risk, distinct from any prepregnancy variation in risk factors, we excluded all women with preexisting hypertension or other risk factors. In addition, we studied the changes in BP in each preeclampsia group, over the 6 to 13 years after pregnancy, relative to booking BP. We found that those who went on to develop early onset disease had a substantially greater increase in BP over the subsequent 6 to 13 years compared with either those who were normotensive during pregnancy or those with late-onset disease. Furthermore, in those with higher BPs at booking, it was only those who went on to develop early onset preeclampsia who had subsequent further elevations of BP. Indeed, those with late-onset disease or normotension during pregnancy had a relative drop in BP. Therefore, the type of preeclampsia seems to predict additional patterns to subsequent postpartum rises in BP than could have been determined by booking BP alone.

The combination of BP measures during the perinatal period with measures in later life also allowed us to use our cohort to distinguish between short-term persistent effects of pregnancy on BP behavior and long-term variation remote from the pregnancy. In some women, it can take 6 months to 2 years for BP levels to normalize after...
delivery.\textsuperscript{3} Previous studies have also found persistent differences in cardiac and vascular responses during this early period\textsuperscript{32} and some specifically investigated differences related to early onset preeclampsia. They found raised BP, impaired endothelial function, and arterial stiffness in women with early onset preeclampsia for 6 to 18 months postpregnancy.\textsuperscript{12,15} Our study confirms these persistent elevations in BP ≤6 weeks after delivery, particularly in those with early onset preeclampsia. Furthermore, our long-term data demonstrate that differences in BP patterns persist beyond this early postnatal period dependent on the time of onset of preeclampsia.

In later life, although formerly preeclamptic women had significantly higher daytime ambulatory BP, only mothers who had early onset preeclampsia had elevated nighttime BP compared with either controls or those with late-onset disease. Elevated nocturnal BP is closely associated with cardiovascular risk both in normotensive and hypertensive subjects.\textsuperscript{29} During pregnancy, women with preeclampsia have a reduced drop in nocturnal BP evident as early as the second trimester,\textsuperscript{30,31} and we have shown previously that the circadian pattern can even reverse in some high-risk pregnancies.\textsuperscript{32} Our current data suggest that early onset preeclampsia in particular is associated with higher nocturnal pressures remote from pregnancy.

We, and others, have demonstrated previously that offspring of pregnancies complicated by preeclampsia have raised BP in childhood and young adulthood,\textsuperscript{33,34} with a predisposition to stroke in later life.\textsuperscript{35} Previous studies have tended to study children grouped according to exposure to preeclampsia without differentiation based on time of onset of the condition. With this analytical approach, those born to preeclamptic pregnancies have around a 2-mm Hg higher BP during childhood.\textsuperscript{34} However, those born preterm to preeclamptic pregnancies have around a 10-mm Hg higher BP,\textsuperscript{36} which raises the question of whether early onset disease, often associated with preterm delivery, may lead to greater BP differences. In our present study, we found that BP differences during childhood were seen exclusively in those born to early onset disease with a 6-mm Hg higher peripheral and central BP. Many in this group were also born preterm and some small for gestational age factors that are linked with higher BP during childhood. Although it is possible that this accounts for the variation, we have shown in previous studies that those born preterm to pregnancies complicated by preeclampsia have specific vascular differences compared with those born to normotensive pregnancies.\textsuperscript{36} Kvehaugen et al\textsuperscript{37} found that endothelial dysfunction after preeclampsia was only evident in mother and offspring when the infant was born small for gestational age. This observation could suggest that severity of placental pathology may be relevant to later outcomes. However, this combination did not determine postpartum BP and metabolic parameters in our mothers or children, only the diagnosis of early onset preeclampsia (Figure 1 and Table S4). Fetal growth restriction may be a better identifier of mothers and offspring exposed to severe placental pathology than small for gestational age. It was not possible from our medical records to identify accurately fetal growth-restricted infants, and this interaction should be considered in future studies. Interestingly, our study shows that mothers who experienced early onset disease were more likely to have been born to early onset preeclampsia themselves, and contains observations that raise the possibility that BP variation, programmed genetically or in utero, may be relevant to familial predisposition to preeclampsia.

Our study sample, particularly of offspring, seems relatively small compared with population-based recruitment strategies that report several thousand mother-offspring pairs.\textsuperscript{38} However, this is, in part, because we used a case note adjudication process to ensure that only those who fulfilled appropriate criteria for preeclampsia and had no preexisting disease relevant to long-term outcomes were recruited. Our sample of 90 subjects with preeclampsia is actually a similar

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Ambulatory blood pressure. A, Women with both early onset (\textcolor{red}{red bars}) and late-onset preeclampsia (PE) (\textcolor{blue}{blue bars}) had significantly greater 24-hour and daytime systolic blood pressure (SBP) compared with controls (\textcolor{green}{green bars}). B, However, only women with early onset preeclampsia had significantly higher nocturnal SBP compared with both women with uncomplicated pregnancies and late-onset preeclampsia (The \textbf{bar graph} represents mean SBP±SEM).}
\end{figure}
size to other reports based on population recruitment and recruited a greater proportion of early onset cases. Because of the study design, our control group was substantially smaller but powered to identify clinically relevant BP variation. Our findings suggest that it would now be of interest to see whether other features of BP response differ between mothers with preeclampsia, such as response to exercise or mental stress. The greatest variation between groups was seen with DBP, and key components of diastolic pressures may warrant further investigation. BP levels were predominantly in the normal range, and further follow-up will be of value to determine which features predispose to hypertension.

In summary, we show that, although all women who have preeclampsia have a greater risk of hypertension and cardiovascular disease in later life, those who develop early onset preeclampsia have several specific adverse BP characteristics after pregnancy. They are more likely to have elevated BP at 6 weeks postpartum, and they have a greater increase in BP relative to their booking BP over the next 10 years and significantly higher nocturnal BP in later life. Furthermore, they are more likely to have been born to a preeclamptic
pregnancy themselves and their offspring have higher BP in childhood. A better understanding of the biological differences that underlie these characteristics may help identify why those with early onset preeclampsia develop more severe later disease and identify targeted approaches to disease prevention.

**Perspectives**

Preeclampsia, affecting 2% to 8% of all pregnancies, is associated with increased risk of hypertension and cardiovascular disease in mother and child. We demonstrate that mothers who developed early onset preeclampsia and their offspring display distinct adverse BP characteristics both during pregnancy and later in life. Because these features precede the development of hypertension, better understanding of the underlying biological differences may help establish why they are more likely to develop cardiovascular disease later and identify targeted approaches to disease prevention.

**Sources of Funding**

This study was funded by grants from the National Institute for Health Research Oxford Biomedical Research Centre and Oxford British Heart Foundation Centre of Research Excellence. Dr Lazard was supported by the Oxford Health Services Research Committee, Dr Leeson by the British Heart Foundation, and A. Shore by the Peninsula National Institute for Health Research Clinical Research Facility.

**Disclosures**

None.

**References**


**Novelty and Significance**

**What Is New?**
- Women who develop early onset preeclampsia, and their offspring, have distinct blood pressure characteristics compared with those with late-onset preeclampsia or normotensive pregnancies.

**What Is Relevant?**
- Persistently higher blood pressure 6 weeks postpartum.
- Greater relative increase in blood pressure between pregnancy and later life.

**Summary**
- Significantly higher nocturnal blood pressures in later life.
- 6-mm Hg greater offspring blood pressure.

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Hypertension. 2012;60:1338-1345; originally published online October 8, 2012; doi: 10.1161/HYPERTENSIONAHA.112.198366

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Data Supplement (unedited) at:
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ONLINE DATA SUPPLEMENT

UNIQUE BLOOD PRESSURE CHARACTERISTICS IN MOTHER AND OFFSPRING FOLLOWING EARLY-ONSET PREECLAMPSIA

Short Title: Lazdam Blood Pressure and Early-Onset Preeclampsia

Merzaka Lazdam MRCPa, Arancha de la Horra MAa,b, Jonathan Diescha, Yvonne Kenworthy BSca,b, Esther Davis MBChBa, Adam J Lewandowski BSca, Cezary Szmieglski MDc, Angela Shore PhDd, Lucy Mackillop MA MRCPb, Rajesh Kharbanda PhD FRCPa, Nicholas Alp PhD DM FRCPa, Christopher Redman MA FRCPb, Brenda Kelly PhD MRCOGb, Paul Leeson PhD FRCPa*

aOxford Cardiovascular Clinical Research Facility, Department of Cardiovascular Medicine, University of Oxford, UK.

bNuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford, UK.

cDepartment of Internal Medicine, Warsaw University Hospital, Warsaw, Poland.

dPeninsula NIHR Clinical Research Facility and Peninsula College of Medicine & Dentistry, University of Exeter, UK.
Table S1. Comparison of responders and non-responders

<table>
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<th>Blood Pressure</th>
<th>Preeclampsia</th>
<th>P Value</th>
<th>Controls</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Non-Responders</td>
<td>Responders</td>
<td>Non-Responders</td>
</tr>
<tr>
<td>N</td>
<td>90</td>
<td>219</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Booking SBP, mmHg</td>
<td>115 (14)</td>
<td>116 (13)</td>
<td>0.55</td>
<td>108 (10)</td>
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<tr>
<td>Booking DBP, mmHg</td>
<td>68 (9)</td>
<td>70 (10)</td>
<td>0.10</td>
<td>64 (8)</td>
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</tbody>
</table>

Data are presented as Mean (SD). Two tailed unpaired student t Test or Chi Square P values reported.

SBP: systolic blood pressure, DBP: diastolic blood pressure.
Table S2. Maternal Blood pressure

<table>
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<tr>
<th>Parameters</th>
<th>Early PE (n 45)</th>
<th>Late PE (n 45)</th>
<th>Controls (n 50)</th>
<th>PE vs. Controls</th>
<th>Early PE vs. Controls</th>
<th>Late PE vs. Controls</th>
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<tr>
<td>Antenatal Blood Pressure (1st Trimester)</td>
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<td></td>
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<tr>
<td>Booking SBP, mmHg</td>
<td>115.70 (14.09)</td>
<td>114.80 (14.34)</td>
<td>108.41 (9.84)</td>
<td>0.02</td>
<td>0.03</td>
<td>0.09</td>
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<td>Booking DBP, mmHg</td>
<td>70.61 (8.73)</td>
<td>66.15 (10.48)</td>
<td>63.83 (8.02)</td>
<td>0.03</td>
<td>0.005</td>
<td>0.38</td>
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<td>Peripheral and Central Blood Pressure 6-13 years post-partum</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>61.85 (9.60)</td>
<td>61.71 (10.90)</td>
<td>60.51 (9.00)</td>
<td>0.48</td>
<td>0.49</td>
<td>0.57</td>
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<td>Peripheral SBP, mmHg</td>
<td>122.04 (14.75)</td>
<td>118.57 (12.95)</td>
<td>110.96 (10.03)</td>
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<td>&lt;0.001</td>
<td>0.001</td>
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<tr>
<td>Peripheral DBP, mmHg</td>
<td>80.31 (9.98)</td>
<td>76.11 (9.48)</td>
<td>72.63 (7.76)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.05</td>
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<td>Central SBP, mmHg</td>
<td>115.86 (15.51)</td>
<td>112.13 (13.45)</td>
<td>104.39 (11.57)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
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<td>Central DBP, mmHg</td>
<td>81.82 (10.11)</td>
<td>78.22 (9.17)</td>
<td>74.39 (8.54)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as Mean (SD). Two tailed unpaired student t Test P values reported.

SBP: systolic blood pressure, DBP: diastolic blood pressure.
<table>
<thead>
<tr>
<th>Parameters of Offspring Born to</th>
<th>Early PE (n 15)</th>
<th>Late PE (n 18)</th>
<th>Controls (n 14)</th>
<th>PE vs. Controls</th>
<th>Early PE vs. Controls</th>
<th>Late PE vs. Controls</th>
</tr>
</thead>
<tbody>
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<td><strong>Birth Characteristics</strong></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Birth Gestation, weeks</td>
<td>33.07 (2.89)</td>
<td>37.67 (1.41)</td>
<td>40.43 (1.02)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth Weight, grams</td>
<td>1819.20 (817.69)</td>
<td>2978.39 (542.01)</td>
<td>3696.43 (489.23)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Born SGA n (%)</td>
<td>7 (46.7)</td>
<td>3 (16.7)</td>
<td>0</td>
<td>0.02</td>
<td>0.003</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Characteristics at Enrolment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>9.13 (1.77)</td>
<td>9.17 (1.65)</td>
<td>9.93 (1.21)</td>
<td>0.13</td>
<td>0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.39 (0.11)</td>
<td>1.40 (0.13)</td>
<td>1.44 (0.11)</td>
<td>0.23</td>
<td>0.22</td>
<td>0.35</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>35.64 (11.30)</td>
<td>33.79 (8.68)</td>
<td>39.70 (11.59)</td>
<td>0.13</td>
<td>0.35</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>70.67 (7.94)</td>
<td>72.25 (9.12)</td>
<td>70.57 (8.51)</td>
<td>0.73</td>
<td>0.98</td>
<td>0.60</td>
</tr>
<tr>
<td>Metabolic Characteristics</td>
<td>(n 9)</td>
<td>(n 13)</td>
<td>(n 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Cholesterol, mmol/L</td>
<td>2.44 (0.47)</td>
<td>2.46 (0.55)</td>
<td>2.39 (0.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total:HDL Cholesterol Ratio</td>
<td>3.17 (1.05)</td>
<td>2.85 (0.39)</td>
<td>2.82 (0.50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.85 (0.51)</td>
<td>0.58 (0.22)</td>
<td>0.87 (0.46)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.57 (0.31)</td>
<td>4.68 (0.37)</td>
<td>4.61 (0.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>5.66 (1.94)</td>
<td>4.67 (1.91)</td>
<td>6.66 (4.70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA IR</td>
<td>1.15 (0.40)</td>
<td>0.99 (0.44)</td>
<td>1.40 (1.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as Mean (SD). Two tailed unpaired student t Test P values reported.

SGA: small for gestational age (<10th centile on birth charts), HDL: high density lipoprotein cholesterol, LDL: Low Density Lipoprotein Cholesterol, HOMA IR: homeostatic model assessment insulin resistance factor
Table S4. The impact of small for gestational age delivery on mother and child

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mothers</th>
<th></th>
<th>Offspring</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGA</td>
<td>AGA</td>
<td>SGA</td>
<td>AGA</td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>59</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.16 (7.12)</td>
<td>27.89 (6.20)</td>
<td>0.20</td>
<td>16.67 (3.39)</td>
</tr>
<tr>
<td>Total Cholesterol, mmol/L</td>
<td>4.91 (1.07)</td>
<td>4.95 (1.01)</td>
<td>0.87</td>
<td>4.06 (0.47)</td>
</tr>
<tr>
<td>HDL Cholesterol, mmol/L</td>
<td>1.46 (0.36)</td>
<td>1.52 (0.37)</td>
<td>0.45</td>
<td>1.51 (0.48)</td>
</tr>
<tr>
<td>LDL Cholesterol, mmol/L</td>
<td>2.93 (0.90)</td>
<td>2.92 (0.88)</td>
<td>0.96</td>
<td>2.23 (0.23)</td>
</tr>
<tr>
<td>Total : HDL Cholesterol</td>
<td>3.47 (0.77)</td>
<td>3.39 (0.90)</td>
<td>0.67</td>
<td>2.87 (0.70)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.12 (0.89)</td>
<td>1.09 (0.44)</td>
<td>0.83</td>
<td>0.67 (0.21)</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>8.35 (4.07)</td>
<td>9.63 (5.91)</td>
<td>0.29</td>
<td>37.43 (16.62)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.81 (0.61)</td>
<td>5.06 (0.45)</td>
<td>0.32</td>
<td>4.53 (0.42)</td>
</tr>
</tbody>
</table>

Data are presented as Mean (SD). Two tailed unpaired student t Test P values reported.

SGA: small for gestational age (<10th centile on birth charts), AGA: appropriate for gestational age, BMI: body mass index, HDL: high density lipoprotein cholesterol, LDL: Low Density Lipoprotein Cholesterol.
Figure S1. Blood pressure characteristics in women who had preeclampsia with a small for gestational age, compared to appropriate for gestational age, infant. There were no differences in booking or post-partum blood pressures, in contrast to the differences identified when time of onset of preeclampsia is used to define groups. A difference in blood pressure is noted in the third trimester which may suggest intra-pregnancy blood pressure differs in the presence of a small for gestational age infant.
†Represents significant comparing preeclamptic women (PE) delivering SGA (small for gestational age) and AGA (appropriate for gestational age).