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Maternal Hemodynamics at 11–13 Weeks of Gestation in Pregnancies Delivering Small for Gestational Age Neonates

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Key Words

Pyramid of prenatal care · Preeclampsia · Arterial stiffness · Small for gestational age · Fetal growth restriction · Pulse wave velocity

Abstract

Objective: To examine aortic systolic blood pressure (SBP_{Ao}), pulse wave velocity (PWV) and augmentation index (adjusted to a heart rate of 75 beats per minute, AIx-75) at 11–13 weeks' gestation in pregnancies delivering small for gestational age (SGA) neonates with and without preeclampsia (PE). ***Methods:*** At 11+0 to 13+6 weeks' gestation, maternal history was recorded and PWV, AIx-75, SBP_{Ao}, uterine artery pulsatility index (PI) and maternal serum pregnancy-associated plasma protein-A (PAPP-A) were measured. We compared women with (n = 337) and without (n = 48) PE that delivered SGA neonates with unaffected controls (n = 6,429). ***Results:*** In the SGA group without PE, compared to unaffected controls, there was no significant difference in AIx-75 (1.03 vs. 1.00 multiple of the median, MoM), PWV (0.98 vs. 1.00 MoM) or SBP_{Ao} (1.01 vs. 1.00 MoM), but uterine artery PI was increased (1.10 vs. 1.00 MoM) and PAPP-A decreased (0.85 vs. 1.00 MoM). In SGA with PE, compared to unaffected controls, there was increased AIx-75 (1.13 vs. 1.00 MoM), SBP_{Ao} (1.09 vs. 1.00 MoM), uterine artery PI (1.40 vs. 1.00 MoM) and decreased PAPP-A (0.72 vs. 1.00 MoM), but no significant difference in PWV (1.05 vs. 1.00 MoM). ***Conclusion:*** In pregnancies with SGA neonates, impaired placentation is reflected in low PAPP-A and high uterine artery PI at 11–13 weeks' gestation. In the SGA group with PE, but not in those without PE, there is increased SBP_{Ao} and AIx-75.

Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are major causes of maternal and perinatal mortality and morbidity [1–4]. PE is commonly associated with FGR, particularly early-onset PE [5]. A common pathophysiological mechanism for PE and FGR is impaired placentation, reflected in increased uterine artery pulsatility index (PI) and reduced maternal serum pregnancy-associated plasma protein-A (PAPP-A) [6–8]. However, the determinant of whether a pregnancy with impaired placentation will be complicated by PE or FGR without PE remains unknown. We hypothesized that the development of PE in cases of impaired placentation is, at least in part, a consequence of pre-pregnancy predisposition to

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development of chronic hypertension. This is analogous to women with predisposition to type 2 diabetes developing gestational diabetes mellitus under the physiological stress of normal pregnancy.

Evidence for increased maternal predisposition to PE is provided by studies which report that women who develop PE are at increased risk of cardiovascular disease and stroke in the subsequent decades [9–12]. Cardiovascular disease is associated with increased arterial stiffness and central aortic systolic blood pressure (SBP_{Ao}) [13–16]. Arterial stiffness can be assessed non-invasively by a simple technique that provides reproducible measurements within a few minutes, and the values of SBP_{Ao}, pulse wave velocity (PWV) and augmentation index (AIx) have been validated against invasive monitoring [17]. In women with established PE, there is an increase in the values of PWV and AIx, which are measures of arterial stiffness [18–22]. Recent studies have reported that in women who develop PE, increased SBP_{Ao} and arterial stiffness are apparent from 11–13 weeks' gestation [23–25].

The objective of this study was to examine the hemodynamic indices of SBP_{Ao}, PWV and AIx and impaired placentation, reflected in increased uterine artery PI and reduced serum PAPP-A at 11–13 weeks' gestation, in pregnancies with and without PE that result in delivery of small for gestational age (SGA) neonates.

Methods

This was part of an ongoing prospective screening study for adverse obstetric outcomes in women attending for their routine first trimester ultrasound scan in pregnancy at University College Hospital and King's College Hospital, London, UK, between December 2009 and February 2011. At this visit, which was held at 11+0 to 13+6 weeks of gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies by measurement of the fetal crown-rump length and nuchal translucency thickness and maternal serum PAPP-A and free β-hCG [26]. We also used transabdominal color Doppler ultrasound to visualize the left and right uterine arteries, measured the PI in each vessel and calculated the mean PI [27]. We used the Arteriograph (TensioMed Ltd., Budapest, Hungary) to measure the AIx, PWV and SBP_{Ao} in all women who agreed to take part in the study [17]. Written informed consent was obtained from all women. The study was approved by the London-Surrey Borders Research Ethics Committee.

The inclusion criteria for this study were women with a singleton pregnancy and a live fetus identified at the 11^{+0}–13^{+6} week scan. We excluded pregnancies with major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks and those that subsequently developed PE and delivered non-SGA neonates.

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), medical and obstetric history including parity (parous or nulliparous if no previous pregnancies delivering at or after 24 weeks). The questionnaire was then reviewed by a doctor together with each woman. The maternal weight and height were measured and the BMI calculated in kilograms per meter squared.

Outcome Measures

Details of maternal characteristics and the findings of the 11–13 week assessment were recorded in our database. Data on pregnancy outcomes were obtained from the maternity computerized records or the women's general practitioners and were recorded in our database. The neonate was considered SGA if the birth weight was less than the 5th percentile for gestational age at delivery, using a reference range derived from our population [28]. Neonates with birth weight at or above the 5th percentile were classified as non-SGA. The diagnosis of PE was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy [29]. In PE, the systolic blood pressure should be ≥140 mm Hg and/or the diastolic blood pressure should be ≥90 mm Hg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women, with proteinuria of ≥300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available.

Arteriograph Measurements

All measurements were performed in a temperature-controlled room (22°C) with participants in the supine position. The Arteriograph cuff was then applied on the left arm over the brachial artery for estimation of SBP_{Ao} (mm Hg), PWV (m/s) and AIx (%) as previously described [30]. All recordings were made by doctors who had received appropriate training on the use of the Arteriograph. The results of PWV, AIx or SBP_{Ao} were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Statistical Analysis

Comparison between the outcome groups was by χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables, both with post hoc Bonferroni correction. Data are presented as median and interquartile ranges (IQR) for continuous data and as numbers with percentages in parentheses for categorical variables.

The distributions of AIx, PWV and SBP_{Ao} were made Gaussian after logarithmic transformation. The normality of distributions was tested using histograms and probability plots after excluding outliers outside three standard deviations. Each value in the SGA and non-SGA groups was expressed as a multiple of the median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the log-transformed value in the multiple regression analysis as previously described [30]. As there was a linear relationship between AIx and heart rate, AIx was adjusted to a heart rate of 75 beats per minute (AIx-75). Pearson correlation analysis was used to examine the association between

Table 1. Maternal characteristics in the outcome groups

Maternal characteristics	Non-SGA (n = 6,429)	SGA without PE (n = 337)	SGA with PE (n = 48)
Maternal age, years	32.0 (28.2–35.4)	31.1 (25.5–34.7)*	31.5 (27.1–36.7)
Maternal weight, kg	64.0 (57.9–72.3)	59.0 (53.2–67.0)*	65.9 (56.9–75.5)
Maternal height, m	1.65 (1.60–1.69)	1.62 (1.56–1.66)*	1.63 (1.58–1.67)*
Maternal BMI	23.5 (21.4–26.4)	22.6 (20.7–25.3)*	24.2 (22.1–27.9)
Crown-rump length, mm	62.4 (57.5–67.7)	61.1 (55.6–66.2)*	63.5 (57.2–68.8)
Ethnicity, n (%)			
Caucasian	4,709 (73.2)	189 (56.1)	26 (54.2)
African	928 (14.4)	77 (22.8)*	18 (37.5)*
South Asian	379 (5.9)	37 (11.0)*	3 (8.3)
East Asian	250 (3.9)	21 (6.2)	0
Mixed	163 (2.5)	13 (3.9)	0
Parity, n (%)			
Nulliparous	3,469 (54.0)	223 (66.2)	32 (66.7)
Parous	2,960 (46.0)	114 (33.8)*	16 (33.3)
Cigarette smoker	360 (5.6)	53 (15.7)*	5 (10.4)
Conception, n (%)			
Spontaneous	6,169 (96.0)	317 (94.1)	44 (91.7)
Ovulation drugs	260 (4.0)	20 (5.9)	4 (8.3)
Gestational age at delivery, weeks	40.1 (39.0–40.9)	39.6 (38.5–40.7)*	36.7 (33.9–38.5)*
Birth weight percentile	48.9 (29.6–69.1)	2.8 (1.4–4.2)*	1.4 (0.4–3.2)*

Values are medians with IQR in parentheses unless otherwise indicated. Comparisons between each outcome group with controls by χ^2 test and Fisher's exact test for categorical variables and Mann-Whitney U test with post hoc Bonferroni correction for continuous variables: * $p < 0.025$.

$\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM, $\log_{10}SBP_{Ao}$ MoM, $\log_{10}$uterine artery PI MoM and $\log_{10}$PAPP-A MoM with gestational age at delivery.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

Maternal PWV, AIx and SBP_{Ao} were successfully recorded in 7,653 singleton pregnancies. We excluded 569 (7.4%) because they had missing outcome data (n = 449), the pregnancies resulted in fetal death or miscarriage before 24 weeks' gestation (n = 60) or the pregnancies were terminated for fetal abnormalities or social reasons (n = 60). In addition, we excluded 270 cases that subsequently developed PE and delivered non-SGA neonates (n = 133) or gestational hypertension (n = 137). In the remaining 6,814 cases, 337 (5.0%) without PE subsequently delivered SGA neonates, 48 (0.7%) with PE delivered SGA neonates and 6,429 (94.30%) delivered non-SGA neonates.

The maternal characteristics of the outcome groups are given in table 1. In the SGA group without PE, compared to the non-SGA group, women were younger, had a lower median maternal height and weight, more women were of African and South Asian racial origin, and there were more nulliparous women who delivered at an earlier gestational age. In the SGA group with PE, compared to the non-SGA group, women had a lower median maternal height, more women were of African racial origin and delivered at an earlier gestational age.

SGA without PE

In the pregnancies without PE that subsequently delivered SGA neonates, compared to those that delivered non-SGA neonates, there was no significant difference in AIx-75, PWV or SBP_{Ao}, but the uterine artery PI MoM was increased and PAPP-A MoM was decreased (table 2; fig. 1).

There was a significant association of $\log_{10}$AIx-75 MoM ($r = -0.122$, $p = 0.025$), $\log_{10}SBP_{Ao}$ MoM ($r = -0.127$, $p = 0.019$) and $\log_{10}$PAPP-A MoM ($r = 0.134$, $p = 0.015$; fig. 2) with gestational age at delivery but not of $\log_{10}$PWV MoM ($r = -0.004$, $p = 0.937$) or $\log_{10}$uterine artery PI MoM ($r = 0.056$, $p = 0.316$; fig. 2) with gestational age at delivery.

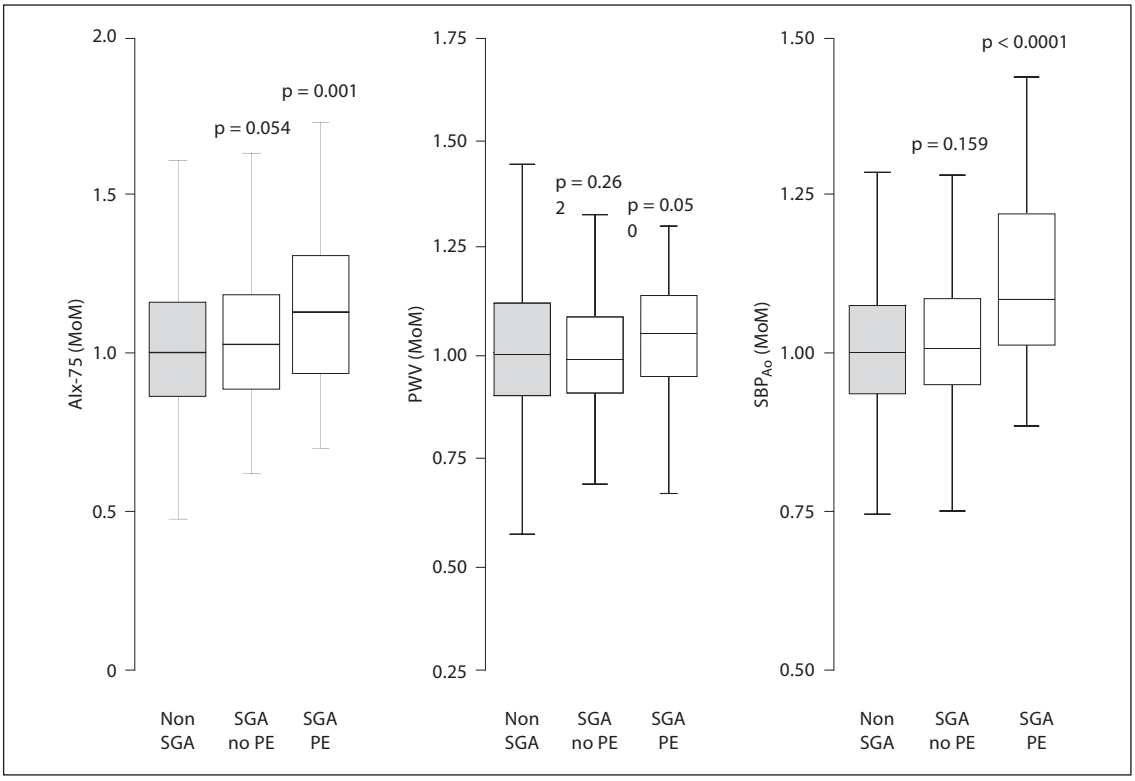

Fig. 1. Box and whisker plots of AIx-75 MoM, PWV MoM, and central SBP MoM in pregnancies with and without PE that subsequently delivered SGA neonates, compared to those that did not. The horizontal line in the box represents the median, the box represents the interquartile range and the whiskers indicate the minimum and maximum values.

Table 2. AIx, PWV and central SBP_{Ao} in pregnancies with and without PE that delivered SGA neonates compared to those that did not

Variable	Non-SGA (n = 6,429)	SGA without PE (n = 337)	SGA with PE (n = 48)
AIx			
%	10.5 (5.4–16.6)	12.5 (6.8–18.8)	14.5 (7.9–22.0)
MoM	1.00 (0.87–1.16)	1.03 (0.89–1.19)	1.13 (0.93–1.32)*
PWV			
m/s	6.56 (5.83–7.42)	6.33 (5.76–7.05)	7.23 (6.54–7.77)
MoM	1.00 (0.90–1.12)	0.98 (0.90–1.09)	1.05 (0.94–1.14)
Central SBP			
mm	108 (101–117)	108 (101–116)	119 (112–132)
MoM	1.00 (0.94–1.08)	1.01 (0.95–1.09)	1.09 (1.01–1.22)*
PAPP-A			
IU/l	2.90 (1.92–4.50)	2.77 (1.67–4.96)	2.16 (1.08–8.07)
MoM	1.00 (0.79–1.42)	0.85 (0.56–1.25)*	0.72 (0.53–0.98)*
Uterine artery PI			
Unit	1.71 (1.39–2.07)	1.93 (1.50–2.30)	2.36 (2.12–2.79)
MoM	1.00 (0.82–1.20)	1.10 (0.86–1.32)*	1.40 (1.17–1.64)*

Values are medians and IQR in parentheses. Comparisons between outcome groups by Mann-Whitney U test and post hoc Bonferroni correction: corrected significance value * $p < 0.025$.

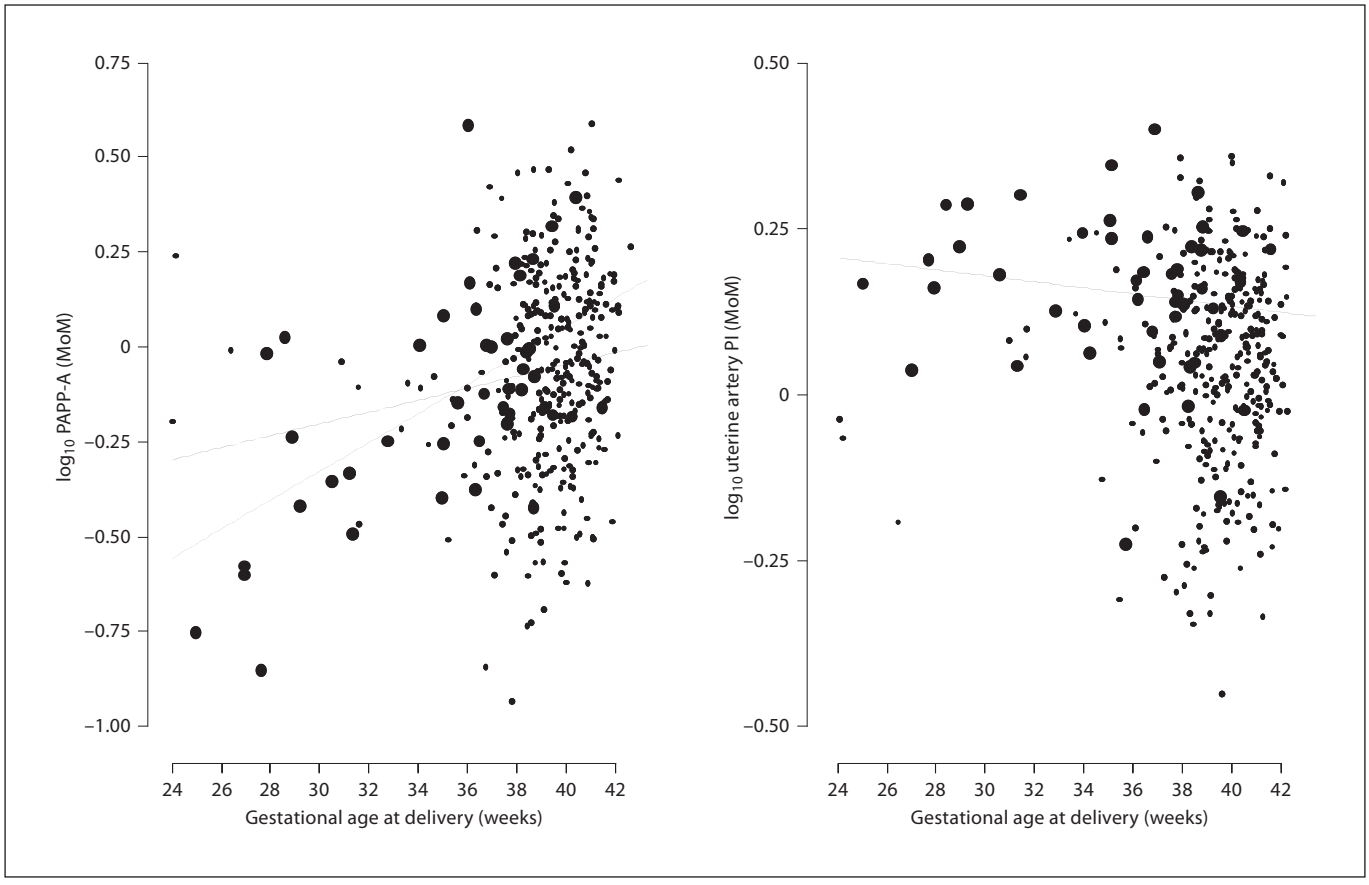

Fig. 2. Scatter plot demonstrating the association of $\log_{10}$PAPP-A MoM (left) and $\log_{10}$uterine artery PI MoM (right) with gestational age at delivery in women without PE that subsequently delivered SGA neonates (closed circles and solid regression line) and those with PE that delivered SGA neonates (open circles and interrupted regression line).

SGA with PE

In the pregnancies with PE that subsequently delivered SGA neonates, compared to those that delivered non-SGA neonates, the AIx-75, SBP_{Ao} and uterine artery PI MoM were increased and PAPP-A MoM was decreased, but the PWV was not significantly different (table 2; fig. 1).

There was a significant association of $\log_{10}$uterine artery PI MoM and $\log_{10}$PAPP-A MoM with gestational age at delivery ($r = -0.333$, $p = 0.022$ and $r = 0.567$, $p < 0.0001$, respectively; fig. 2) but not of $\log_{10}$AIx-75 MoM, $\log_{10}$PWV MoM or $\log_{10}SBP_{Ao}$ MoM with gestational age at delivery ($r = 0.0004$, $p = 0.998$; $r = 0.078$, $p = 0.599$ and $r = -0.053$, $p = 0.720$, respectively).

Discussion

The findings of this study demonstrate that in pregnancies delivering SGA neonates, there is evidence of impaired placentation reflected in low PAPP-A and high uterine artery PI at 11–13 weeks' gestation. In the SGA group with PE, but not in those without PE, there is increased SBP_{Ao} and arterial stiffness. The findings are compatible with our hypothesis that in pregnancies with impaired placentation, one of the determinants of whether there will be development of PE or SGA without PE is pre-existing susceptibility to cardiovascular disease reflected in increased SBP_{Ao} and AIx-75.

Impaired trophoblastic invasion of the maternal spiral arteries leads to placental ischemia and the release of inflammatory factors which cause endothelial cell activation and damage [31, 32]. There is also evidence that

women who are predisposed to cardiovascular disease prior to pregnancy are likely to have a degree of generalized endothelial dysfunction and low-grade inflammation, manifested as increased arterial stiffness [33–35]. It is possible that the clinical manifestations of PE are the consequence of a synergy of two independent factors, placental ischemia and predisposition to cardiovascular disease, producing an exaggerated degree of endothelial dysfunction.

The strengths of this study include the large number of subjects examined and the narrow gestational age range of 11–13 weeks for the investigation, which is emerging as the first clinical visit in pregnancy for assessment of patient-specific risks for a wide range of pregnancy complications [36]. Robust outcome data were collected prospectively, the diagnosis of PE was ascertained from the patients' records, and we controlled for potential confounders that might affect arterial stiffness and SBP_{Ao}. The birth weight percentiles were calculated using a reference range derived from our population [28]. A limitation of the study is the lack of longitudinal data before pregnancy, during pregnancy and postnatally in women who had SGA with PE in order to evaluate whether increased arterial stiffness and SBP_{Ao} pre-existed and/or persisted beyond the pregnancy.

SGA was defined as neonatal birth weight less than the 5th percentile for gestational age at delivery, using a reference range derived from our population [28]. This group might include constitutionally small babies, as well as growth-restricted fetuses. We could not study the changes in these two subgroups separately. The study was based on screening at 12 weeks and subsequent outcome with retrospective diagnosis of SGA based on birth weight. We did not examine all these women in the third trimester and therefore we do not have Doppler measurements in the third trimester in the majority of the SGA cases.

Evidence that women who develop PE are at increased risk of cardiovascular disease and stroke in the subsequent decades is derived from large epidemiological studies [9–12]. There is also evidence from healthy non-pregnant individuals that increased arterial stiffness and SBP_{Ao} are associated with subsequent development of cardiovascular disease and death [37–41]. It is therefore possible that, firstly, the abnormal cardiovascular findings in early pregnancy in women who subsequently develop PE may actually predate conception and, secondly, development of PE in cases of impaired placentation is, at least in part, a consequence of pre-pregnancy predisposition to development of chronic hypertension.

In pregnancies complicated by SGA without PE, there is evidence of impaired placentation, but in these cases, we found that arterial stiffness and SBP_{Ao} at 11–13 weeks are normal. Epidemiological studies reported that the long-term risk of mortality from cardiovascular disease was inversely related to the birth weight of offspring [42, 43]. However, these studies did not present separate data for SGA with and without PE and it is therefore not possible to determine whether the observed increase in mortality could be attributed to the subgroup of SGA with associated PE. A retrospective cohort study of 129,290 women reported that the hazard ratio for hospital admission or death from ischemic heart disease was 1.9 in those who delivered a baby in the lowest birth weight quintile for gestational age in the absence of PE [44]. A nationwide Swedish study on 923,686 women and their first singleton births between 1983 and 2005 reported that the increase in hazard ratio for maternal hospitalization or death from cardiovascular disease, adjusted for pregnancy characteristics including PE, was modest (1.83, 95% CI 1.59–2.11) and confined to those with very small infants whose birth weight was below the 2nd percentile [45]. Suggested possible explanations for such a link between birth of an SGA neonate and increased susceptibility to cardiovascular disease include environmental, lifestyle or common genetic risk factors [44].

In pregnancies delivering SGA neonates, with or without coincidence of PE, there is evidence of impaired placentation. Similarly, epidemiological studies suggest that both women who develop PE and those who deliver SGA neonates in the absence of PE are at increased risk of death from cardiovascular disease. Our finding that in women who develop PE, but not in those delivering SGA neonates in the absence of PE, there is evidence of increased SBP_{Ao} and arterial stiffness, suggests that the mechanisms underlying the increased risk of cardiovascular disease in the two types of pregnancies may be different.

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