Ultrasound Obstet Gynecol 2012; **40**: 35–39
Published online 15 June 2012 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.11154

Maternal hemodynamics at 11–13 weeks of gestation and preterm birth

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KEYWORDS: arterial stiffness; central systolic blood pressure; pregnancy; preterm birth; pulse wave velocity

ABSTRACT

Objective *Women who experience preterm birth (PTB) are at increased risk of cardiovascular morbidity and mortality in the subsequent decades. Individuals with cardiovascular disorders have increased central aortic systolic blood pressure (SBP_{Ao}) and arterial stiffness, assessed by pulse wave velocity (PWV) and augmentation index (AIx). The aim of this screening study was to evaluate SBP_{Ao}, PWV and AIx at 11–13 weeks' gestation in women who delivered preterm.*

Methods *This was a prospective study in singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation. Maternal history and characteristics were recorded, and PWV, AIx and SBP_{Ao} were measured. We compared these parameters in women who had spontaneous (*n = *244) or iatrogenic (*n = *110) PTB before 37 weeks' gestation and before 34 weeks with those in women who had term delivery (*n = *7489).*

Results *Compared with women who had term delivery, women who had iatrogenic PTB had significantly higher AIx (1.08 (interquartile range (IQR), 0.91–1.27) multiples of the median (MoM), vs. 1.00 (IQR, 0.86–1.16) MoM) and SBP_{Ao} (1.06 (IQR, 0.98–1.15) MoM vs. 1.00 (IQR, 0.93–1.07) MoM). However, there was no significant difference in AIx, PWV or SBP_{Ao} between those who had spontaneous PTB and those who had term delivery. These findings were similar for those who had PTB at < 34 and < 37 weeks' gestation.*

Conclusion *Women who had iatrogenic PTB, but not those who had spontaneous PTB, have increased SBP_{Ao} and arterial stiffness that is apparent from as early as the first trimester of pregnancy.* *Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Preterm birth (PTB), which is the leading cause of perinatal mortality and morbidity, is also associated with increased risk of maternal long-term cardiovascular disease and early death[1–8]. In non-pregnant women with cardiovascular disease there is increased arterial stiffness and central aortic systolic blood pressure (SBP_{Ao})[9,10], and there is evidence that these hemodynamic changes may precede the onset of the disease[11–15].

There is substantial evidence linking pregnancy complications, such as pre-eclampsia (PE) and gestational diabetes mellitus (GDM), with cardiovascular disorders later in life. Several studies reported increased arterial stiffness and SBP_{Ao} in women with clinically established PE and GDM[16–19]. It has been demonstrated recently that SBP_{Ao} and arterial stiffness measured at 11–13 weeks' gestation are increased in women who later develop PE and GDM[20–23].

The aim of this study was to assess arterial stiffness and SBP_{Ao} at 11–13 weeks' gestation in women who subsequently had PTB and to compare the findings in spontaneous and iatrogenic delivery, where the underlying cause is mainly PE.

METHODS

This was part of a 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 March 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

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Accepted: 10 November 2011

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(CRL) and nuchal translucency (NT) thickness and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG)[24,25]. The Arteriograph (TensioMed Ltd., Budapest, Hungary) was used to measure the augmentation index (AIx), pulse wave velocity (PWV) and SBP_{Ao}. Written informed consent was obtained from all women agreeing to participate in the study. The study was approved by the London–Surrey Borders Research Ethics Committee.

In this study we investigated maternal hemodynamics in pregnancies resulting in PTB and compared these with the maternal hemodynamics in pregnancies delivering at term. The inclusion criteria for this study were singleton pregnancy delivering a phenotypically normal neonate. We excluded pregnancies ending in termination or miscarriage.

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 history (including prepregnancy chronic hypertension or diabetes mellitus type 1 or 2) and obstetric history including parity (parous or nulliparous if no previous pregnancies delivering at or after 24 weeks) and previous PTB (< 37 weeks' gestation). The questionnaire was then reviewed by a doctor together with each woman. The maternal weight and height were measured and the body mass index (BMI) was calculated in kg/m^2.

Study outcomes

Iatrogenic delivery was defined as induced vaginal birth or Cesarean birth without onset of labor. Spontaneous delivery was defined as vaginal delivery without induction of labor or Cesarean section following spontaneous onset of labor.

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 from the women's general practitioners and were also recorded in our database. The records of women who had PTB were examined to ascertain the type of and indication for PTB. The birth weight percentile for gestation at delivery was calculated using a reference range derived from our population[26].

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} (mmHg), PWV (m/s) and AIx (%), as previously described[22]. 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 made using the chi-square test or Fisher's exact test for categorical variables and using the Mann–Whitney *U*-test for continuous variables. Data are presented as median and interquartile range (IQR) for continuous data and as *n* (%) 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 3 SD. Each value in the PTB and non-PTB groups was expressed as a multiple of the median (MoM) after adjustment for those characteristics was found to provide a substantial contribution to the log-transformed value in the multiple regression analysis, as previously described[22]:

$$\begin{aligned}
&\text{Log}_{10}\text{ expected AIx-75} = -0.007\\
&\quad + [0.004 \times (\text{maternal age in years} - 30)]\\
&\quad - [0.001 \times (\text{maternal weight in kg} - 66)]\\
&\quad - [0.264 \times (\text{maternal height in m} - 1.65)];\\
&\quad R^2 = 0.096,\ P < 0.0001.\\
&\text{Log}_{10}\text{ expected PWV} = -0.042\\
&\quad + [0.003 \times (\text{maternal age in years} - 30)]\\
&\quad + [4.4e^{-03} \times (\text{maternal weight in kg} - 66)]\\
&\quad + [0.441 \times (\log_{10}\text{ mean arterial pressure})];\\
&\quad R^2 = 0.121,\ P < 0.0001.\\
&\text{Log}_{10}\text{ expected } SBP_{Ao} = 2.036\\
&\quad + [0.001 \times (\text{maternal weight in kg} - 66)];\\
&\quad R^2 = 0.097,\ P < 0.0001.
\end{aligned}$$

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

RESULTS

Maternal PWV, AIx and SBP_{Ao} were successfully recorded in 8327 singleton pregnancies. We excluded 484 (5.8%) because they had missing outcome data ($n = 349$), the pregnancies resulted in fetal death or miscarriage before 24 weeks' gestation ($n = 79$) or the pregnancies were terminated for fetal abnormalities or for social reasons ($n = 56$). In the remaining 7843 cases, 354 (4.5%) subsequently had PTB < 37 weeks, 124 (1.6%) delivered at < 34 weeks' gestation and 7489 (95.5%) delivered at term (≥ 37 weeks). Women who had PTB at < 37 weeks' gestation were subdivided into 244 (3.1%) who had

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spontaneous PTB and 110 (1.4%) who had iatrogenic PTB. In the spontaneous PTB group, 163 (66.8%) women presented with uterine contractions and 81 (33.2%) with preterm prelabor membrane rupture. In those with iatrogenic PTB the indication for delivery was severe PE and/or fetal growth restriction (FGR) ($n = 82$, 74.5%), antepartum hemorrhage caused by placental abruption ($n = 8$) or placenta previa ($n = 9$), fetal distress ($n = 9$), maternal malignancy ($n = 1$) and alloimmune thrombocytopenia ($n = 1$). Similarly, women who had PTB at < 34 weeks' gestation were subdivided into 83 (1.1%) who had spontaneous PTB and 41 (0.5%) who had iatrogenic PTB.

The maternal characteristics of the outcome groups are given in Table 1. In the spontaneous preterm group (< 37 weeks), compared with the term group, there were more women of non-Caucasian racial origin, more parous women who had a previous spontaneous PTB and more women who delivered a neonate with higher birth-weight percentile at an earlier gestational age. Compared with the term group, the medically indicated preterm group (< 37 weeks) had more women of African ethnic origin, more women who had assisted conception, more women who had chronic hypertension, more parous women who had a previous iatrogenic PTB and more women who delivered a neonate with a lower birth weight percentile at an earlier gestational age.

In the women with iatrogenic PTB at < 37 weeks, compared with those who delivered at ≥ 37 weeks, AIx and SBP_{Ao} were higher but there was no significant difference in PWV (Table 2). There was no significant difference in AIx, PWV or SBP_{Ao} in the women with spontaneous PTB at < 37 weeks compared with those who delivered at term. Similarly, increased AIx and SBP_{Ao} were observed in women with iatrogenic PTB at < 34 weeks, but not in those with spontaneous PTB at < 34 weeks (Table 2).

DISCUSSION

The findings of this study at 11–13 weeks' gestation demonstrate that in women with subsequent PTB, arterial stiffness and SBP_{Ao} are significantly increased if the PTB was iatrogenic but not if it was spontaneous. Our findings were similar in women who experienced PTB at < 37 weeks and at < 34 weeks. Consequently, the previously noted association between PTB and subsequent cardiovascular disorders is likely to be related to those who had iatrogenic delivery mainly for PE and FGR.

The strengths of this study include the large number of subjects and the narrow gestational range of 11–13 weeks, which is emerging as the first clinical visit in pregnancy for assessment of patient-specific risks for a wide range of pregnancy complications[27]. Outcome data were collected prospectively, the type of and indication

Table 1 Maternal characteristics in the outcome groups

Maternal characteristic	*Term* (n = *7489*)	*Spontaneous PTB* (n = *244*)	*Iatrogenic PTB* (n = *110*)
Maternal age (years)	31.9 (28.0–35.3)	31.0 (27.4–35.6)	32.4 (27.8–36.6)
Maternal weight (kg)	64.1 (57.9–72.6)	63.5 (56.9–74.9)	65.5 (57.4–75.0)
Maternal height (m)	1.65 (1.60–1.69)	1.65 (1.60–1.69)	1.64 (1.60–1.68)
Maternal body mass index (kg/m^2)	23.6 (21.4–26.6)	23.7 (21.0–27.9)	23.9 (21.7–27.4)
Crown–rump length (mm)	62.3 (57.4–67.5)	61.3 (56.8–66.5)	60.4 (56.4–64.7)*
Gestational age at recruitment (weeks)	12.6 (12.3–13.0)	12.6 (12.2–12.9)	12.5 (12.2–12.8)*
Ethnicity			
Caucasian	5370 (71.7)	149 (61.1)	62 (56.4)
African	1174 (15.7)	56 (23.0)*	35 (31.8)*
South Asian	473 (6.3)	18 (7.4)*	7 (6.4)
East Asian	284 (3.8)	12 (4.9)*	4 (3.6)
Mixed	188 (2.5)	9 (3.7)*	2 (1.8)
Parity			
Nulliparous	4093 (54.7)	130 (53.3)	70 (63.6)
Parous	3396 (45.3)	114 (46.7)	40 (36.4)
Cigarette smoker	447 (6.0)	19 (7.8)	6 (5.5)
Conception			
Spontaneous	7182 (95.9)	233 (95.5)	100 (90.0)*
Ovulation drugs	307 (4.1)	11 (4.5)	10 (9.1)*
Chronic hypertension	68 (0.9)	2 (0.8)	7 (6.4)*
Pre-existing diabetes	34 (0.5)	3 (1.2)	1 (0.9)
Previous spontaneous PTB	202 (3.1)	36 (14.8)*	5 (4.5)
Previous iatrogenic PTB	33 (0.5)	0.0	4 (3.6)*
Gestational age at delivery (weeks)	40.1 (39.2–41.0)	35.5 (33.2–36.4)*	34.8 (32.3–36.2)*
Birth weight (g)	3410 (3116–3730)	2454 (1950–2820)*	1918 (1460–2320)*
Birth weight percentile	47.5 (25.9–69.3)	53.5 (26.3–76.2)*	10.0 (1.2–34.8)*

Data are given as median (interquartile range) or *n* (%). *$P < 0.025$: comparison was made *vs* control for each outcome group (chi-square test and Fisher's exact test for categorical variables and Mann–Whitney *U*-test with post-hoc Bonferroni correction for continuous variables). PTB, preterm birth < 37 weeks' gestation.

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Table 2 Comparison of variables in pregnancies delivered preterm (PTB) before 37 weeks and before 34 weeks with pregnancies delivered at or after 37 weeks

		PTB < 37 weeks		*PTB < 34 weeks*	
Variable	*Delivery ≥ 37 weeks (n = 7489)*	*Spontaneous (n = 244)*	*Iatrogenic (n = 110)*	*Spontaneous (n = 83)*	*Iatrogenic (n = 41)*
AIx					
Percent	10.71 (5.52–16.88)	10.03 (4.51–15.75)	12.73 (6.96–20.36)*	8.45 (2.16–14.34)	13.50 (8.89–20.92)*
MoM	1.00 (0.86–1.16)	0.99 (0.84–1.16)	1.08 (0.91–1.27)*	0.95 (0.81–1.11)	1.11 (0.95–1.28)*
PWV					
m/s	6.57 (5.85–7.46)	6.56 (5.92–7.36)	6.77 (6.06–7.68)	6.45 (5.79–7.43)	6.81 (6.28–7.84)
MoM	1.00 (0.90–1.12)	1.00 (0.91–1.10)	1.01 (0.91–1.12)	0.99 (0.90–1.11)	1.03 (0.92–1.14)
SBP_{Ao}					
mmHg	109 (101–117)	110 (102–118)	116 (107–126)*	111 (103–122)	116 (107–127)*
MoM	1.00 (0.93–1.07)	1.01 (0.94–1.09)	1.06 (0.98–1.15)*	1.04 (0.95–1.12)	1.07 (0.98–1.15)*

Comparisons between outcome groups and term deliveries by Mann–Whitney *U*-test with *post hoc* Bonferroni correction for continuous variables. *$P < 0.025$. AIx, augmentation index; MoM, multiples of the median; PWV, pulse wave velocity; SBP_{Ao}, central aortic systolic blood pressure.

for PTB were ascertained from the patients' records and we controlled for maternal factors that might affect arterial stiffness and SBP_{Ao}[22]. A limitation of the study was the lack of longitudinal data during pregnancy and postnatally in women who had PTB in order to evaluate whether increased arterial stiffness and SBP_{Ao} persisted beyond the pregnancy.

Our results offer a possible explanation for the reported association between PTB and increased susceptibility to cardiovascular disease and early death[1–8] because increased AIx and SBP_{Ao} are markers of cardiovascular risk and endothelial dysfunction. The association between increased arterial stiffness and SBP_{Ao} in the group with iatrogenic PTB is not surprising because in the majority of these cases the reason for delivery was PE. Pregnancy has been proposed to be a challenge test which reveals pathology in women with preclinical risk factors[28]. It is possible that cardiovascular morbidity and the conditions that require iatrogenic PTB share common causes or risk factors, such as raised blood pressure, endothelial dysfunction, insulin resistance and dyslipidemia. In this respect, the early delivery was a marker of the severity of this pre-existing pathology rather than a cause or copathology.

Most studies reporting on the association between PTB and increased susceptibility to cardiovascular disease and early death did not distinguish between iatrogenic and spontaneous delivery[1–6,8]. Women with metabolic syndrome diagnosed in the first trimester of pregnancy were reported to have a three-fold increased risk for PTB, which was significant for iatrogenic PTB but not for spontaneous PTB[29]. An epidemiological study involving 3506 women demonstrated an association between prepregnancy blood pressure, glucose, triglycerides and PTB, but these associations were significantly reduced after adjustment for hypertensive disorders in pregnancy[30]. Another epidemiological study of 750 350 women demonstrated independent associations between PTB and death from ischemic heart disease with hazard ratios of 2.5 for iatrogenic PTB and 2.1 for spontaneous PTB[7]. Similarly, a study of 129 290 women reported that the hazard ratio for death from ischemic heart disease in women who had PTB was 6.4 in those where the PTB was associated with PE and 1.9 in those without PE[2]. In another epidemiological study of 626 272 women, those who had PTB were at increased risk of death from cardiovascular causes and the increase was 8.1-fold in those where the PTB was associated with PE and three-fold in those without PE[3].

Our findings indicate that women who had PE and/or FGR severe enough to require iatrogenic PTB, but not those who had spontaneous PTB, have increased arterial stiffness and SBP_{Ao} that is apparent from as early as the first trimester of pregnancy. This is consistent with the results of previous studies which reported that women with PTB are at increased risk of later development of cardiovascular disease.

ACKNOWLEDGMENT

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No.: 1037116).

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