Association of chronic hypertension with birth of small for gestational age neonates

Anca M. Panaitescu[1], Ahmet A. Baschat,[2] Ranjit Akolekar,[1,3] Argyro Syngelaki,[1] Kypros H. Nicolaides[1]

1. Department of Fetal Medicine, King's College Hospital, London, UK.
2. Johns Hopkins Center for Fetal Therapy, Baltimore, USA
3. Department of Fetal Medicine, Medway Maritime Hospital, Kent, UK.

Short Title: Chronic hypertension and birth weight

Correspondence
Professor KH Nicolaides,
Fetal Medicine Research Institute,
King's College Hospital,
16-20 Windsor Walk,
Denmark Hill, London SE58BB
Telephone: +442032998256
Fax: +442077339534
email: kypros@fetalmedicine.com

Acknowledgement: This study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116).

ABSTRACT

Objective: To examine the effect of chronic hypertension (CH), with and without superimposed preeclampsia (PE), on the incidence of small for gestational age (SGA) neonates, and explore possible mechanisms for such association.

Methods: The data for the study were derived from prospective screening for adverse pregnancy outcomes in women with singleton pregnancies attending for their first routine hospital visit at 11-13 weeks' gestation, which included recording of maternal characteristics and medical history and measurement of mean arterial pressure (MAP). Birth weight z-score, adjusted for gestational age and for maternal and pregnancy characteristics, and incidence of SGA were compared between those with and without CH in the total population and in the subgroups with and without PE. Regression analysis was used to examine the relationship between MAP and birth weight z-score and incidence of SGA and PE in those with and without CH.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17553

Results: The study population constituted 74,226 pregnancies, including 1,052 (1.4%) with CH and 73,174 without CH. Preeclampsia developed in 233 (22.1%) cases of the group with CH and in 1,662 (2.3%) of those without CH. In the group that developed PE, there was no significant difference between those with CH and those without CH in either the median birth weight z-score or the incidence of SGA. In the group without PE, the incidence of SGA was twice as high in those with than in those without CH. There was a significant association between $\log_{10}$ MAP multiple of the median and incidence of SGA and PE which was more marked in those with CH than in those without CH.

Conclusion: CH is associated with increased risk of SGA and PE and this is related to MAP at 11-13 weeks' gestation.

Keywords: Chronic hypertension; birth weight; preeclampsia; small for gestational age.

Introduction

Chronic hypertension (CH) is found in 1-2% of pregnancies and in such women the incidence of small for gestational age (SGA) neonates, after adjustment for potential confounding variables from maternal characteristics, medical and obstetric history, is twice as high than in women without CH.[1] However, it is uncertain whether the observed increased risk of SGA in pregnancies with CH is the direct consequence of the disease itself and / or its treatment or it is due to the association with a high incidence of superimposed preeclampsia (PE), which is >20% in those with CH and only 2% in those without CH, and that CH in the absence of PE does not increase the risk of SGA.[2]

The objective of this study is first, to examine the effect of CH, with and without superimposed PE, on birth weight and the incidence of SGA neonates, and second, explore possible mechanisms underlying the association between CH and SGA.

Methods

Study population

This was a prospective screening study for adverse obstetric outcomes in pregnant women attending for their first routine hospital visit at King's College Hospital, London, UK (between March 2006 and July 2015) and Medway Maritime Hospital, Kent, UK (between February 2007 and November 2015). This visit, which was held at 11^{+0}-13^{+6} weeks' gestation, included recording of maternal demographic characteristics and obstetric and medical history, measurement of maternal weight and height, ultrasound examination for the measurement of the fetal crown-rump length (CRL) to determine gestational age,[3] examination of the fetal anatomy for the diagnosis of major fetal defects,[4] and recoding of mean arterial pressure (MAP) by validated automated devices and standardized protocol.[5]

Written informed consent was obtained from women who agreed to participate in the study, which was approved by the Ethics Committee of each participating Hospital. Data on pregnancy outcomes were collected from the hospital maternity records and the women's general medical practitioners. The inclusion criteria for this study were singleton pregnancies examined at 11^{+0}-13^{+6} weeks of gestation, resulting in the live birth or stillbirth of non-malformed babies at $\geq$24 weeks' gestation. We excluded pregnancies with fetal aneuploidies or major defects diagnosed either prenatally or in the neonatal period, pregnancies ending in miscarriage and those ending in termination for psychosocial reasons.

Outcome measures

Women were subdivided into those with CH and those without CH based on their medical history reported at the 11-13 weeks visit. The diagnosis of PE was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.[6] The systolic blood pressure should be $\geq$140 mm Hg and/or the diastolic blood pressure should be $\geq$90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in a previously normotensive woman and in addition there should be significant proteinuria ($\geq$300 mg in 24 hours, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimen, if no 24-hour

collection is available). In pregnancies with CH, diagnosis of superimposed PE requires the development of significant proteinuria after 20 weeks' gestation in a previously non proteinuric woman.

Birth weight was expressed as a z-score which was calculated as a difference between observed and expected birth weight, divided by the fitted standard deviation. The expected birth weight was calculated after adjustment for gestational age and maternal characteristics from our population of phenotypically normal neonates born alive at $\geq$24 weeks' gestation.[7]

Statistical Analysis

Data for continuous variables were expressed as median and interquartile range (IQR). Mann-Whitney U-test was used to examine the significance of difference between continuous variables and χ^2 test or Fisher's exact test was used for categorical variables.

In pregnancies that developed PE, the relationship between birth weight z-score with gestational age at delivery was assessed using regression analysis and slope and intercepts of the regression lines were compared for those with CH and those without CH. In pregnancies without PE, comparison of median birth weight z-score, adjusted for gestational age and for maternal and pregnancy characteristics, between those with and without CH was carried out by Mann-Whitney U-test. The proportion of SGA pregnancies $<5^{th}$ and $<10^{th}$ percentile was determined in those with and without CH and the significance of difference in proportions was examined by χ^2 test. Similarly, the relationship between MAP, expressed as a multiple of the median (MoM) adjusted for maternal characteristics,[8] and birth weight z-score was examined using regression analysis and the significance of difference between slope and intercepts between the two groups was assessed. Comparison of slopes between regression lines in the two groups was carried out by introducing interaction terms in the regression analysis and if there was no significant difference between slopes in the two groups, then a comparison of intercepts of the regression lines was assessed by examining the coefficient [95% confidence intervals (CI)] for CH.[9,10] Logistic regression analysis was used to estimate the risk of delivering an SGA neonate $<5^{th}$ and $<10^{th}$ percentile from MAP MoM values in those with CH and those without CH. Similarly, logistic regression analysis was used to estimate the risk of delivering with PE from MAP MoM values in those with CH and in those without CH.

The statistical software package SPSS Statistics 20.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

Study population

The study population satisfying the inclusion criteria constituted 74,226 pregnancies, including 1,052 (1.4%) with CH and 73,174 without CH. Preeclampsia developed in 233 (22.1%) cases of the group with CH and in 1,662 (2.3%) of those without CH. Maternal characteristics, medical and obstetric history in pregnancies with and without CH are compared in Table 1.

Birth weight z-score and incidence of SGA

In the total population, there was a significant difference between those with CH and those without CH in both the median birth weight z-score ($p<0.0001$) and the incidence of SGA <5th percentile (12.2% vs. 6.1%; $p<0.0001$) and <10th percentile (19.4% vs. 11.5%; $p<0.0001$; Table 2; Figure 1). Similarly, in the group that did not develop PE, there was a significant difference between those with CH and those without CH in both the median birth weight z-score ($p=0.012$) and the incidence of SGA <5th percentile (10.3% vs. 5.7%; $p<0.0001$) and <10th percentile (16.5% vs. 11.1%; $p<0.0001$; Table 2; Figure 1).

In the group that developed PE, there was no significant difference between those with CH and those without CH in either the median birth weight z-score ($p=0.694$) or the incidence of SGA <5th percentile (18.9% vs. 20.5%; $p=0.576$) and <10th percentile (29.2% vs. 28.9%; $p=0.916$). Similarly, there was no significant difference between the two groups in either the slope (standard error 0.026, $p=0.731$) or the intercept (standard error 0.088, $p=0.184$) of the regression lines describing the relationship between birth weight z-score and gestational age at delivery with PE (Figure 2).

Relationship between MAP and risk of SGA

There was a significant association between MAP MoM and birth weight z-score in those with CH ($r=-0.20$, $p<0.0001$) and in those without CH ($r=-0.02$, $p<0.0001$) and there was a significant difference in the slope ($p<0.0001$) and intercept ($p<0.0001$) of the regression line between those with and those without CH (Figure 3).

Logistic regression analysis demonstrated that in patients with CH there was a significant association between $\log_{10}$ MAP MoM and risk of delivering a SGA neonate <5th percentile ($y=-2.469 + 7.366 \log_{10}$ MAP MoM; Nagelkerke $R^2=0.024$, $p<0.0001$; Figure 4) and a SGA neonate <10th percentile ($y=-1.852 + 7.727 \log_{10}$ MAP MoM; Nagelkerke $R^2=0.032$, $p<0.0001$; Figure 4). Similarly, in patients without CH there was a significant association between $\log_{10}$ MAP MoM and risk of delivering a SGA neonate <5th percentile ($y=-2.827 + 2.961 \log_{10}$ MAP MoM; Nagelkerke $R^2=0.002$, $p<0.0001$; Figure 4) and a SGA neonate <10th percentile ($y=-2.084 + 2.151 \log_{10}$ MAP MoM; Nagelkerke $R^2=0.001$, $p<0.0001$; Figure 4).

Relationship between MAP and risk of PE

Logistic regression analysis demonstrated that in patients with CH there was a significant association between $\log_{10}$ MAP MoM and risk of delivering with PE ($y=-1.703 + 8.144 \log_{10}$ MAP MoM; Nagelkerke $R^2=0.037$, $p<0.0001$; Figure 4). Similarly, in

patients without CH there was a significant association between $\log_{10}$ MAP MoM and risk of delivering with PE (y=-3.919 + 16.784 $\log_{10}$ MAP MoM; Nagelkerke R^2=0.044, p<0.0001; Figure 4).

Discussion

Principal findings of this study

The findings of this study demonstrate that in pregnancies with CH, compared to those without CH, there is a two-fold increase in incidence of SGA neonates and 10-fold increase in the incidence of PE. In pregnancies that did not develop PE the incidence of SGA <5th percentile was 10.3% in those with CH and 5.7% in those without CH, whereas in pregnancies that developed PE the incidence of SGA was about 20% in both groups. Consequently, the increase in SGA in pregnancies with CH is partly due to the association of CH with a high incidence of superimposed PE, but it is primarily the consequence of the disease itself.

The incidence of SGA and PE in all pregnancies increased with the level of MAP at 11-13 weeks' gestation and this increase was particularly marked in women with CH. This raises the possibility that higher first trimester maternal blood pressure (BP) directly affects placental development and that the threshold for placental damage is significantly lowered by CH.

Strengths and limitations

The strengths of this study are first, prospective examination of a large population of pregnancies with and without CH, second, use of a standardized protocol for measurement of MAP and expression of the values as MoMs after adjustment for factors that affect the measurements,[5,8] and third, expression of birth weights as z-scores, adjusted for gestational age and maternal characteristics.[7] Potential limitations are the lack of longitudinal BP observations and the relationship of treatment on study outcomes.

Comparison with previous studies

The relationship between maternal BP and fetal growth has primarily been examined in the context of second or third trimester treatment studies for women with CH or gestational hypertension. As a result of these studies, the American College of Obstetricians and Gynecologists (ACOG) recommends that patients with CH should receive antihypertensive medication only if the disease is severe with systolic blood pressure (BP) of ≥160 mm Hg or diastolic BP of ≥110 mm Hg, but not if the disease is mild to moderate with systolic BP of 140-159 mm Hg or diastolic BP of 90-109 mm Hg.[11] Similarly, in the UK, the National Institute for Health and Clinical Excellence (NICE) guideline recommends the use of antihypertensive drugs only when the BP is greater than 150/100 mm Hg.[12] The basis for the reluctance to recommend therapy in mild to moderate disease is that reduction in BP or the drugs themselves may have an adverse effect on fetal growth with an estimated decrease in birth weight by 145 g for every 10 mm decrease in MAP.[13,14] However, in these meta-analyses most patients had gestational hypertension, rather than CH and in most studies therapy was initiated in the

late second or early third trimester. A recent Cochrane review of all randomised trials evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy reported that therapy was associated with halving in the risk of developing severe hypertension, but there was no significant effect on the risk of PE or SGA.[15] A multicenter trial involving 987 women at a median gestational age of 24 (range 14-33) weeks, with CH or gestational hypertension and diastolic BP of 90-105 mm Hg, compared a policy of tight control in BP with a target diastolic BP of 85 mm Hg with a policy of less-tight control with target diastolic BP of 100 mm Hg; development of severe hypertension was lower in the tight-control group but there was no significant difference between the two policies in incidence of PE or SGA.[16]

A secondary analysis of a randomized trial on low-dose aspirin for prevention of PE in high-risk women enrolled at a median gestational age of 19 weeks,[17] examined the relation of pre-enrolment BP with pregnancy outcome in 759 women with CH.[18] The rate of SGA <10th percentile increased from 9% for those with pre-enrolment BP <140/90 mm Hg to 12% for BP140–150/90–99 mm Hg and 24% for BP 151–159/100–109 mm Hg; similarly, there was an increase in the incidence of superimposed PE from 21% to 30% and 42%, respectively.[18]

Clinical implications of the study

In CH there is remodeling of small arterial resistance vessels leading to relative thickening of the muscular media, vasoconstriction and decreased capacity for vasodilation.[19-22] In the first trimester of pregnancy trophoblast invasion is not yet complete and the maternal uterine arteries still possess a muscular wall that is potentially susceptible to the adverse effects of high BP. It could be postulated that, in the presence of such impaired placental vasculature, maintenance of normal intervillous oxygenation necessitate a relatively high perfusion pressure during the second and third trimesters; consequently, lowering the BP during this time may have an adverse effect on fetal growth[13,14] or at least not decrease the high rates in PE and SGA observed in pregnancies with CH.[15,16]

The extent to which in CH normalization of BP in the first trimester could improve placentation and prevent PE and SGA remains to be determined.

References

1. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcomes: a cohort study. *Ultrasound Obstet Gynecol* 2017; doi: 10.1002/uog.17493.

2. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, Farnot U, Bergsjø P, Bakketeig L, Lumbiganon P, Campodónico L, Al-Mazrou Y, Lindheimer M, Kramer M; World Health Organization Antenatal Care Trial Research Group. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol* 2006; **194**: 921-931.

3. Robinson HP, Fleming JE: A critical evaluation of sonar crown rump length measurements. *BJOG* 1975; **182**: 702–710.

4. Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH: Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. *Prenat Diagn* 2011; **31**: 90–102.

5. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther* 2012; 31: 42-48.

6. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.

7. Poon LC, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birth weight in live births and stillbirths. *Ultrasound Obstet Gynecol* 2016; **48**: 602-606.

8. Wright A, Wright D, Ispas A, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 698-706.

9. Potthoff R. A non-parametric test of whether two simple regression lines are parallel. *Ann Statist* 1974; **2**: 295–310.

10. Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. 4th ed; 2002. Blackwell Science.

11. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122**: 1122-1131.

12. NICE. Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE Clinical Guideline 107. Manchester, UK: National Institute for Health and Clinical Excellence, 2011: 1–53.

13. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in

mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000; **355**: 87-92.

14. von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. *J Obstet Gynaecol Can* 2002; **24**: 941-945.

15. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014; **2**: CD002252.

16. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Lee T, Logan AG, Ganzevoort W, Welch R, Thornton JG, Moutquin JM. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015; **372**: 407-417.

17. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, VanDorsten P, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998; **338**: 701–705.

18. Ankumah NA, Cantu J, Jauk V, Biggio J, Hauth J, Andrews W, Tita AT. Risk of adverse pregnancy outcomes in women with mild chronic hypertension before 20 weeks of gestation. *Obstet Gynecol* 2014; **123**: 966-972.

19. Winquist RJ, Webb RC, Bohr DF. Vascular smooth muscle in hypertension. *Fed Proc* 1982; **41**: 2387-2393.

20. Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension* 1989; **13**: 968-972.

21. Heagerty AM, Aalkjaer C, Bund SJ, Korsgaard N, Mulvany MJ. Small artery structure in hypertension. Dual processes of remodeling and growth. *Hypertension* 1993; **21**: 391-397.

22. Touyz RM. Molecular and cellular mechanisms regulating vascular function and structure-implications in the pathogenesis of hypertension. *Can J Cardiol* 2000; **16**: 1137-1146.

Figure legends

Figure 1. Box and whisker plots of birth weight z-score in those with CH (black box) and those without CH (white box) in the total population (left) and in the group that did not develop PE (right).

Figure 2. Individual points and regression lines describing the relationship between birth weight z-score and gestational age at delivery with PE in patients with CH (red dots and line) and those without CH (black dots and line).

Figure 3. Association between MAP MoM and birth weight z-score in pregnancies with CH (red dots and regression line) and in those without CH (black dots and black regression line).

Figure 4. Relationship of MAP MoM with risk of delivering a SGA neonate (left) or developing PE (right) in pregnancies with CH (red lines) and in those without CH (black lines).

Table 1. Maternal characteristics, medical and obstetric history in pregnancies with and without chronic hypertension

Maternal characteristics	**Chronic hypertension (n=1,052)**	**No chronic hypertension (n=73,174)**
GA at recruitment (weeks), median (IQR)	12.7 (12.3 – 13.1)	12.7 (12.3-13.1)
Age (years), median (IQR)	34.5 (30.7 – 38.3)**	30.9 (26.4 – 34.7)
Weight (kg), median (IQR)	82.0 (69.0 – 95.4)**	67.0 (59.2 – 77.3)
Height (cm), median (IQR)	164.4 (160.0 – 168.2)	164.2 (160.0 – 168.9)
Racial origin		
Caucasian, n (%)	511 (48.6)	53,637 (73.3)
Afro-Caribbean, n (%)	470 (44.7)**	13,135 (18.0)
South Asian, n (%)	43 (4.1)	3,091 (4.2)
East Asian, n (%)	11 (1.0)*	1,415 (1.9)
Mixed, n (%)	17 (1.6)	1,896 (2.6)
Method of conception		
Spontaneous, n (%)	1,014 (96.4)	70,945 (97.0)
Ovulation drugs, n (%)	14 (1.3)	759 (1.0)
In vitro fertilization, n (%)	24 (2.3)	1,470 (2.0)
Cigarette smoking, n (%)	75 (7.1)**	7,438 (10.2)
History of SLE / APS, n (%)	11 (1.0)**	134 (0.2)
History of diabetes mellitus		
Type I, n (%)	15 (1.4)**	290 (0.4)
Type II, n (%)	50 (4.8)**	347 (0.5)
Family history of preeclampsia, n (%)	104 (9.9)**	2,877 (3.9)
Family history of diabetes mellitus		
First degree, n (%)	207 (19.7)**	8,923 (12.2)
Second degree, n (%)	73 (6.9)	6,261 (8.6)
Obstetric history		
Nulliparous, n (%)	334 (31.7)	34,998 (47.8)
Previous preeclampsia, n (%)	237 (22.5)**	2,189 (3.0)
Previous SGA <10th, n (%)	130 (12.4)**	4,465 (6.1)

GA = gestational age; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; SGA = birth weight <10th percentile.

*p<0.05
**p<0.01

Table 2. Birth weight z-score and incidence of small for gestational age neonates in pregnancies with and without chronic hypertension

Group	N	Birth weight z-score		Incidence of small for gestational age			
		Median (IQR)	p	<5th percentile	p	<10th percentile	p
Total group							
No CH	73,174	0.001 (-0.681 to 0.717)		4,443 (6.1%)		8,394 (11.5%)	
CH	1,052	-0.109 (-0.991 to 0.570)	<0.0001	128 (12.2%)	<0.0001	203 (19.4%)	<0.0001
No PE group							
No CH	71,512	0.010 (-0.667 to 0.721)		4,102 (5.7%)		7,913 (11.1%)	
CH	819	-0.022 (-0.834 to 0.621)	0.012	84 (10.3%)	<0.0001	135 (16.5%)	<0.0001
PE group							
No CH	1,662	-0.452 (-1.366 to 0.444)		341 (20.5%)		481 (28.9%)	
CH	233	-0.577 (-1.415 to 0.357)	0.694	44 (18.9%)	0.576	68 (29.2%)	0.916

CH = chronic hypertension; PE = preeclampsia; IQR = interquartile range

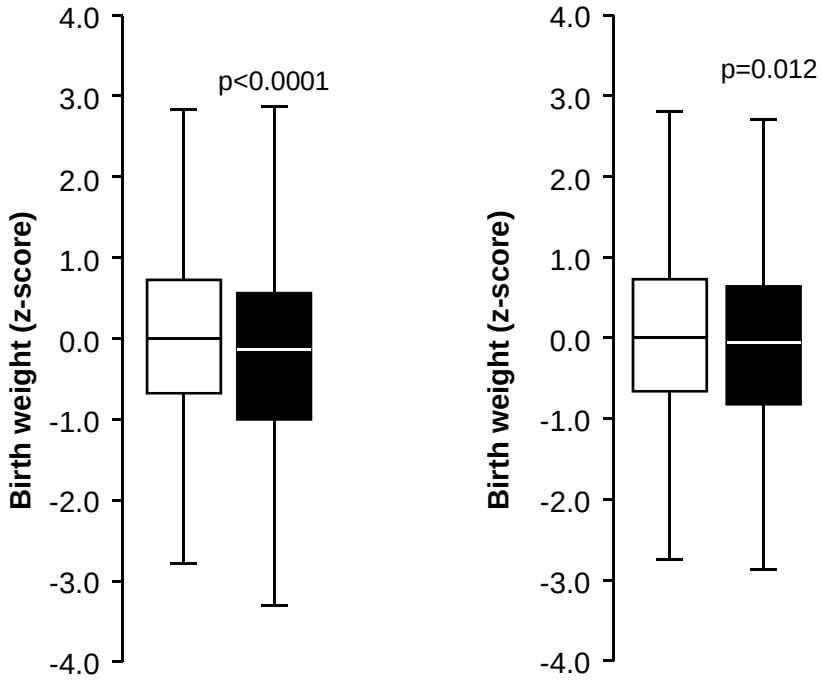

Figure 1

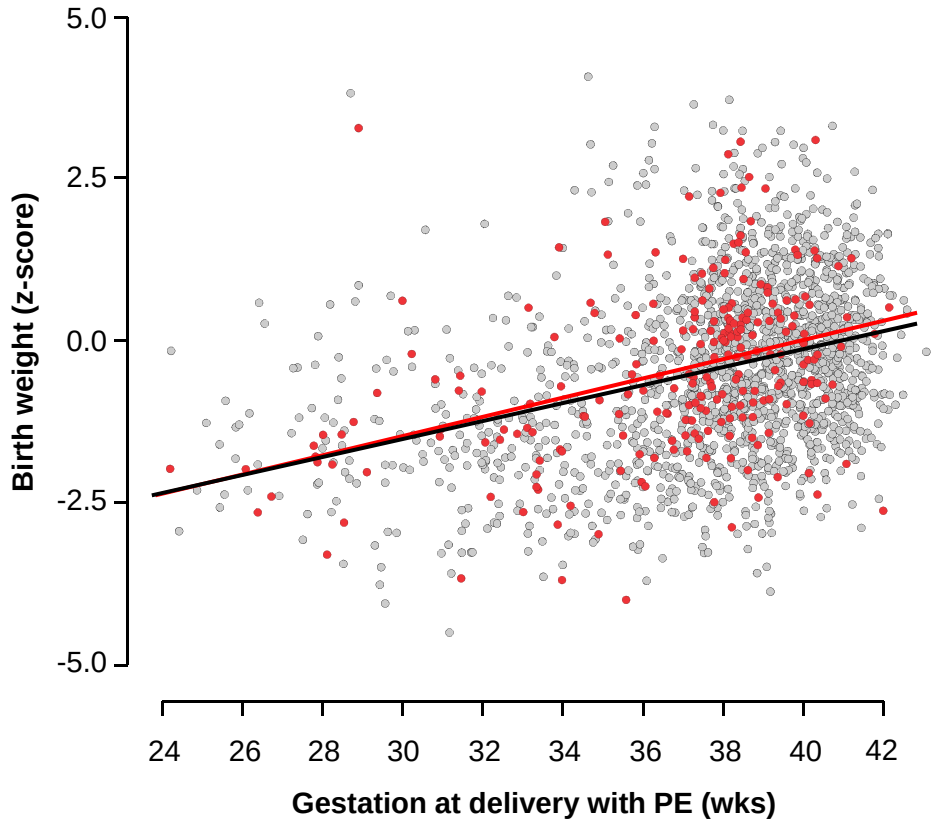

Figure 2

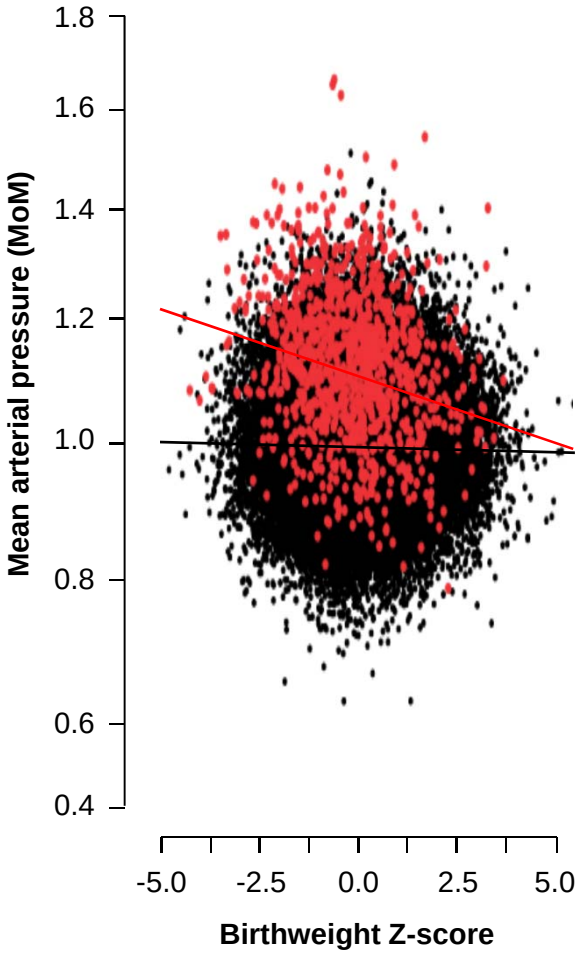

Figure 3

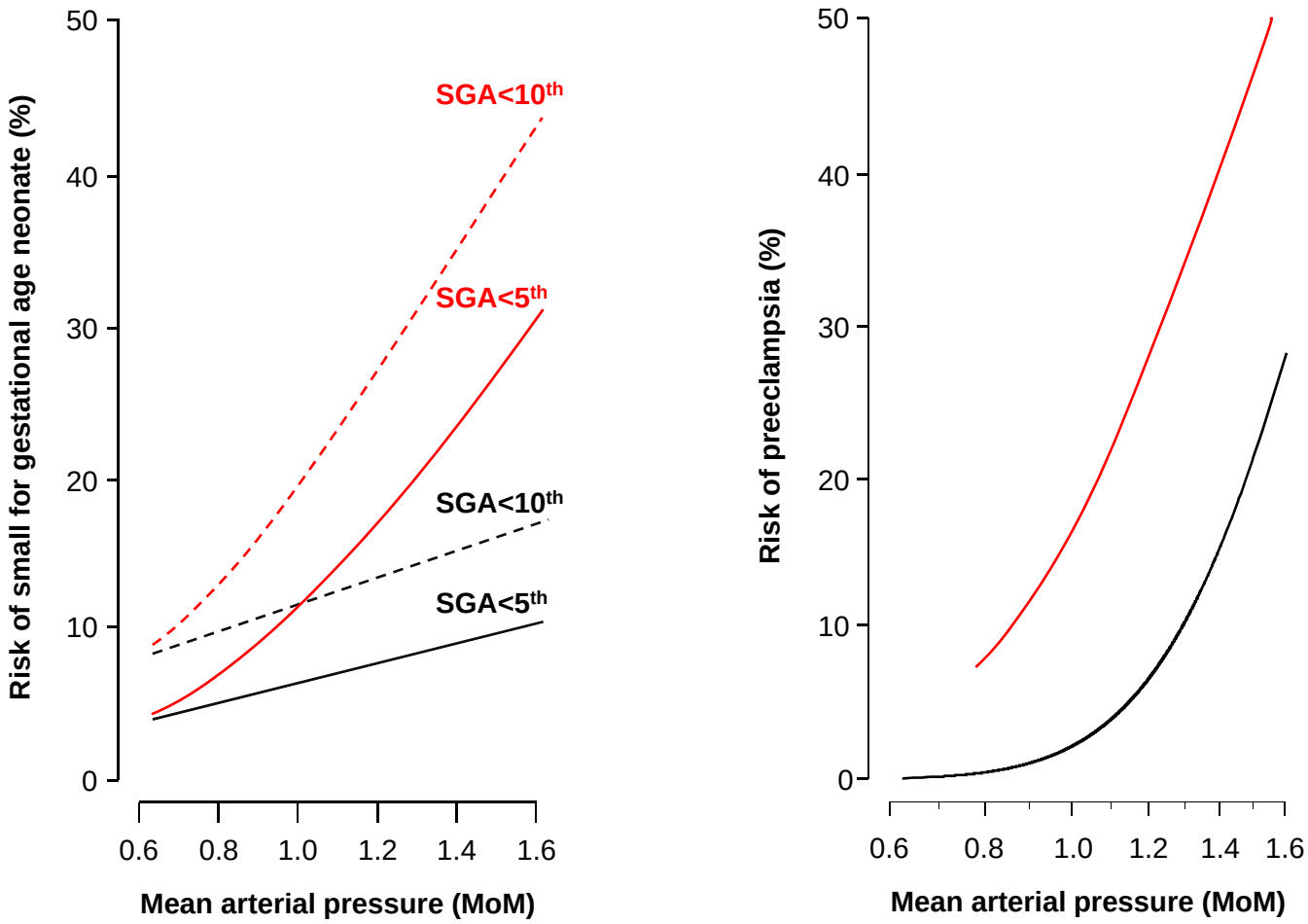

Figure 4