Impaired placentation in women with chronic hypertension that develop preeclampsia

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Short Title: Chronic hypertension and pregnancy complications

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ABSTRACT

Objective: To compare the degree of impaired placentation in pregnancies which develop preeclampsia (PE) in women with and without chronic hypertension (CH).

Methods: The data for this study were derived from prospective screening for adverse pregnancy outcomes in women with singleton pregnancies attending for their first routine hospital visit at 11^{+0}-13^{+6} weeks' gestation. This visit included recording of maternal characteristics and medical history and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum pregnancy associated plasma protein-A (PAPP-A). The measured biomarkers were converted to multiples of the median (MoM) after adjustment for pregnancy characteristics and MoM values in women with CH that developed PE (n=283) were compared to those of women without CH that developed PE (n=2,236).

Results: In both groups with and without CH the measurements of MAP and UTPI were increased, whereas those of PLGF and PAPP-A were decreased and the deviation from normal in all biomarkers decreased with advancing gestational age at delivery with PE. There was no significant difference between those with and without CH in the slope of

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the regression line of Log_{10} MoM biomarker values with gestational age at delivery with PE for any of the biomarkers. However, there was a significant difference in the intercepts and coefficients of biomarkers in the two groups; in the CH group, compared to those without CH, the MAP MoM was higher ($p<0.0001$), UTPI MoM was lower ($p=0.004$), placental growth factor MoM was higher ($p=0.001$) and PAPP-A MoM was higher ($p=0.015$).

Conclusion: In pregnancies that develop PE the degree of impaired placentation, reflected in high UTPI and low PLGF and PAPP-A at 11-13 weeks' gestation, is less in women with than without CH.

Key Words: Chronic hypertension; preeclampsia; uterine artery pulsatility index; serum placental growth factor; serum pregnancy associated plasma protein-A; mean arterial pressure.

Introduction

Preeclampsia (PE) complicates 2-3% of pregnancies and the risk for PE , increases with advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by *in vitro* fertilization and medical history of chronic hypertension (CH), diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome[1] The greatest risk factor for PE is medical history of CH, which is found in 1-2% of pregnancies; the risk of both preterm and term PE, after adjustment for maternal demographic characteristics, medical history and obstetric history, is 5-6 times higher in women with CH than in those without CH.[2]

In PE, particularly preterm PE, there is impairment in the physiologic process of trophoblastic invasion of the maternal spiral arteries and their remodeling from tortuous narrow muscular vessels into large non-muscular channels.[3-5] Reduced perfusion of the placenta causes oxidative stress that triggers off release of trophoblast-derived factors, which enter the maternal circulation and cause generalized endothelial dysfunction and an exaggerated inflammatory response that underlines many of the changes observed in PE.[6-11] In some women with medical disorders, such as CH, there is endothelial dysfunction even before pregnancy and it was proposed that in such cases PE can develop in the absence of impaired placentation; the pre-existing endothelial dysfunction is exacerbated by the physiological burden of pregnancy, as normal pregnancies carry a low-grade systemic inflammatory response.[12-15]

The aim of this study in pregnancies that developed PE was to examine possible differences between women with and without CH in measures of impaired placental perfusion, assessed by uterine artery Doppler, and placental function, reflected in decreased maternal serum levels of placental growth factor (PLGF) and pregnancy associated plasma protein-A (PAPP-A) at 11-13 weeks' gestation.

Methods

The data for this study were derived from prospective screening for adverse outcomes in women with singleton pregnancies 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 of gestation, included recording of maternal characteristics and medical history[1] and measurements of uterine artery pulsatility index (UTPI) by transabdominal color Doppler ultrasound,[16] mean arterial pressure (MAP) by validated automated devices and standardized protocol,[17] and serum concentration of PLGF and PAPP-A (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA). Gestational age was determined from the measurement of the fetal crown-rump length.[18] 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 pregnancies that developed PE and delivered phenotypically normal babies that were live born or stillborn at $\geq$24 weeks' gestation. The diagnosis of PE was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.[19] The systolic blood pressure should be $\geq$140 mm

Hg and/or the diastolic blood pressure should be ≥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 (≥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 CH diagnosis of superimposed PE requires the development of significant proteinuria after 20 weeks' gestation in a previously non proteinuric woman.

Statistical analysis

Comparison of the maternal characteristics and obstetric history between pregnancies with and without CH was by the χ2-square test or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables, respectively.

The measured MAP, UTPI, PLGF and PAPP-A were converted to multiples of the median (MoM) after adjustment for maternal characteristics and medical history. [20-23] Regression analysis was used to determine the association between the MoM values of each biomarker and gestational age at delivery with PE and the slope and intercepts of the regression lines were compared for pregnancies with and without CH. Comparison of slopes between regression lines in the two groups was carried out with Pothoff analysis by introducing interaction terms in the linear regression analysis.[24] 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) for CH.[25]

The statistical software package SPSS Statistics 20.0 (SPSS Inc., Chicago, Ill., USA) and MedCalc Statistical Software version 17.2 (MedCalc Software bvba, Ostend, Belgium) were used for data analyses.

Results

During the study period, first-trimester screening was carried out in 283 pregnancies with CH that developed PE and 2,236 pregnancies without CH that developed PE. Delivery at <37 weeks' gestation occurred in 35.7% (102 of 286) of the CH group and in 27.0% (615 of 2,274) in those without CH. The maternal characteristics and medical and obstetric history of the two groups are compared in Table 1. In pregnancies with CH, compared to those without CH, the median maternal age and weight were higher, and there was a higher incidence of women of Afro-Caribbean racial origin, those with medical history of SLE/APS and type II diabetes mellitus and parous women with a previous pregnancy with PE.

There was no significant difference between those with and without CH in the slope of the regression line of Log_{10} MoM biomarker values with gestational age at delivery with PE for MAP (p=0.282), UTPI (p=0.138), PLGF (p=0.115) or PAPP-A (p=0.435) (Table 2). However, there was a significant difference in the intercepts and coefficients of biomarkers in the two groups; in the CH group, compared to those without CH, the MAP MoM was higher (p<0.0001), UTPI MoM was lower (p=0.004), placental growth factor MoM was higher (p=0.001) and PAPP-A MoM was higher (p=0.015) (Figure 1).

Discussion

Principal findings of this study

The findings of this study demonstrate that in pregnancies that develop PE both in women with CH and in those without CH, at 11-13 weeks' gestation first, MAP and UTPI are increased and PLGF and PAPP-A are decreased, and second, the deviation from normal in these biomarkers decreases with advancing gestational age at delivery with PE and they are therefore greater for early than late PE. The slope of the relationship between biomarker levels with gestational age at delivery is similar in those with CH and those without CH, but for the same severity of PE, reflected in the gestational age at delivery, in the CH group the deviation in UTPI, PLGF and PAPP-A is lower. In pregnancies with CH the MAP at 11-13 weeks' gestation is inevitably considerably higher in those with than without CH.

The findings of the study provide support for the hypothesis that in medical conditions with coexisting endothelial dysfunction, such as CH, the degree of placental impairment necessary to trigger off the development of PE may be less than in pregnancies without such preexisting endothelial dysfunction.[12,13]

Strengths and limitations

The strengths of this study for PE are first, examination of a large population of pregnancies with and without CH that developed PE, second, use of a specific methodology and appropriately trained doctors to measure UTPI and MAP, third, use of automated machines to provide accurate measurement of maternal serum concentration of metabolites that have been shown to be altered in pregnancies associated with impaired placentation, fourth, expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements, and fifth, comparison of levels of biomarkers in women with and without CH by taking into account the gestational age at delivery with PE.

A limitation of the study is that we did not include measurement of potential biomarkers of inflammation and endothelial dysfunction. In previous studies we reported that at 11-13 weeks' gestation in pregnancies that develop PE there are increased maternal circulating levels of the inflammatory factors pentraxin 3, matrix metalloproteinase-9 and the soluble receptor-1 of the tumor necrosis factor-α, as well as P-selectin, a marker of platelet activation.[26-29] We found that the altered levels in these biomarkers were not associated with the degree of impairment in placental perfusion reflected in UTPI. However, we did not investigate whether there are differences in the levels of these biomarkers between pregnancies with CH and those without CH.

Comparison with previous studies

Several studies have documented that development of PE is associated with first-trimester increase in UTPI and MAP and decrease in serum PLGF and PAPP-A.[16,30-35] In this study we compared biomarker levels in women with and without CH. Previous studies have documented the association between CH and endothelial dysfunction and inflamation.[36,37] However, we could not identify reports comparing first-trimester biomarkers in PE in women with and without CH.

Clinical implications of the study

The incidence of CH is 1-2% and in these women the risk of PE is >20%; in this respect a history of CH is the strongest risk factor for PE, compared to other factors in maternal demographic characteristics and medical history.[1,2] Effective first-trimester screening for PE is provided by a combination of maternal factors and MAP, UTPI, PLGF and PAPP-A.[34,35] In pregnancies with CH that develop PE, the smaller deviation from normal in UTPI, PLGF and PAPP-A is compensated by the considerably higher MAP. The rationale for first-trimester prediction of PE from a combination of maternal factors and biomarkers[33,34] is that pharmacological intervention with low-dose aspirin in the high-risk group could potentially reduce the incidence of the disease.[38,39] It is uncertain whether the potential benefit from low-dose aspirin is mediated through an effect on improving placentation or through its anti-inflammatory properties and the extent to which this medication will be equally effective in prevention of PE in pregnancies with and without CH remains to be determined.

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Table 1. Maternal characteristics and medical history in pregnancies with PE in women with and without CH.

Maternal characteristics	**Chronic hypertension (n=283)**	**No chronic hypertension (n=2,236)**
GA at recruitment (weeks), median (IQR)	12.6 (12.3-13.1)	12.6 (12.3-13.1)
Age (years), median (IQR)	34.7 (31.0-38.7) **	30.6 (25.9-34.8)
Weight (kg), median (IQR)	85.0 (71.0-98.0) **	72.0 (62.8-85.0)
Height (cm), median (IQR)	163 (160-168)	163 (159-168)
Racial origin		
Caucasian, n (%)	113 (39.9)	1,394 (62.3)
Afro-Caribbean, n (%)	154 (54.4) **	655 (29.3)
South Asian, n (%)	11 (3.9)	103 (4.6)
East Asian, n (%)	3 (1.1)	36 (1.6)
Mixed, n (%)	2 (0.7)	48 (2.1)
Method of conception		
Spontaneous, n (%)	268 (94.7)	2,125 (95.0)
Ovulation drugs, n (%)	5 (1.8)	27 (1.2)
In vitro fertilization, n (%)	10 (3.5)	84 (3.8)
Cigarette smoking, n (%)	18 (6.4)	166 (7.4)
History of SLE / APS, n (%)	7 (2.5) **	6 (0.3)
History of diabetes mellitus		
Type I, n (%)	4 (1.4)	19 (0.8)
Type II, n (%)	13 (4.6) **	19 (0.8)
Family history of PE	28 (9.9)	176 (7.9)
Family history of diabetes mellitus		
First degree, n (%)	54 (19.1)	369 (16.5)
Second degree, n (%)	25 (8.8)	161 (7.2)
Obstetric history		
Nulliparous, n (%)	95 (33.6)	1,440 (64.4)
Parous with previous PE, n (%)	87 (30.7) **	254 (11.4)
Parous without previous PE, n (%)	101 (35.7) **	542 (24.2)

GA = gestational age; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; PE = preeclampsia. **p<0.0001

Table 2. Pothoff analysis for comparison of slopes of regression lines in pregnancies with and without chronic hypertension for relationship of each biomarker with gestational age at delivery.

Variables in equation	Coefficient (95% CI)	Error	P value
MAP			
Intercept	0.077 (0.055 to 0.099)	0.011	<0.0001
Gestational age	-0.001 (-0.002 to -0.001)	0.0001	<0.0001
Chronic hypertension	0.073 (0.015 to 0.131)	0.030	0.014
Chronic hypertension x GA	-0.001 (-0.002 to 0.001)	0.001	0.282
UTPI			
Intercept	0.539 (0.465 to 0.611)	0.037	<0.0001
Gestational age	-0.013 (-0.015 to -0.011)	0.001	<0.0001
Chronic hypertension	0.115 (-0.073 to 0.302)	0.095	0.230
Chronic hypertension x GA	-0.004 (-0.009 to 0.001)	0.003	0.138
PLGF			
Intercept	-0.889 (-1.030 to -0.748)	0.072	<0.0001
Gestational age	0.020 (0.016 to 0.023)	0.002	<0.0001
Chronic hypertension	-0.254 (-0.647 to 0.139)	0.200	0.205
Chronic hypertension x GA	0.009 (-0.002 to 0.019)	0.005	0.115
PAPP-A			
Intercept	-0.587 (-0.724 to -0.450)	0.070	<0.0001
Gestational age	0.013 (0.010 to 0.017)	0.002	<0.0001
Chronic hypertension	0.189 (-0.179 to 0.557)	0.187	0.314
Chronic hypertension x GA	-0.004 (-0.014 to 0.006)	0.005	0.435

GA = Gestational age; MAP = Mean arterial pressure; UTPI = Uterine artery pulsatility index; PLGF = Placental growth factor; PAPP-A = Pregnancy associated plasma protein-A.

Figure legend

Figure 1. Scatter diagram and regression line for the relationship between mean arterial pressure, uterine artery pulsatility index, serum placental growth factor and pregnancy associated plasma protein-A multiple of the median (MoM) and gestational age at delivery in pregnancies with preeclampsia with chronic hypertension (red circles and red lines) and without chronic hypertension (grey circles and grey lines).

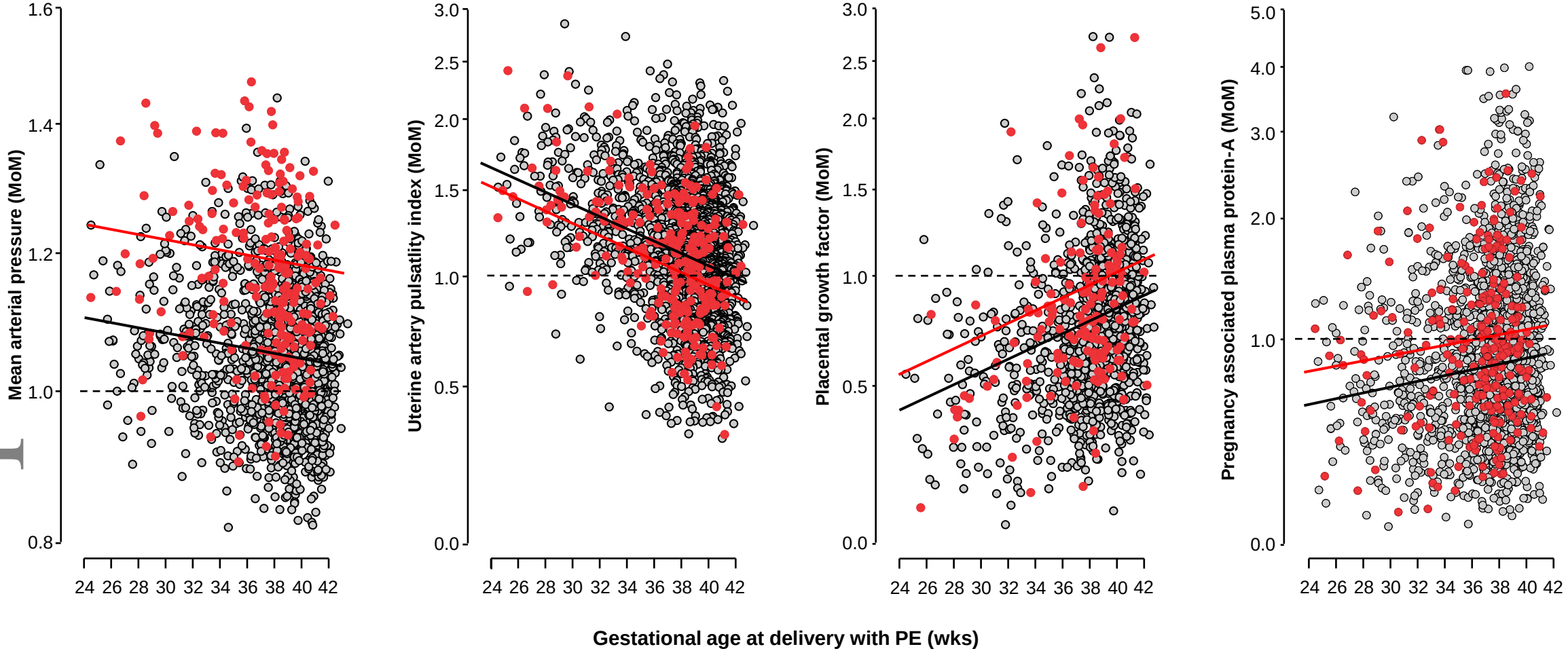

Figure 1