Pregnancy, Hypertension, and Preeclampsia

Adverse Perinatal Outcomes and Risk Factors for Preeclampsia in Women With Chronic Hypertension
A Prospective Study

Lucy C. Chappell, Stephen Enye, Paul Seed, Annette L. Briley, Lucilla Poston, Andrew H. Shennan

Abstract—Prospective contemporaneous data on the outcome of pregnancies in women with chronic hypertension are sparse. Indices of maternal and perinatal morbidity and mortality were determined in 822 women with chronic hypertension with data prospectively collected and rigorously validated. The incidence of superimposed preeclampsia was 22% (n=180) with early-onset preeclampsia (≤34 weeks gestation) accounting for nearly half of these cases. Delivering an infant <10th customized birthweight centile complicated 48% (87/180) of those with superimposed preeclampsia and 21% (137/642) in those without (relative risk [RR] 2.30; 95% confidence intervals [CI] 1.85 to 2.84). Delivery at <37 weeks gestation occurred in 51% of those with superimposed preeclampsia (98% of these iatrogenic) and 15% without (66% iatrogenic) (RR 3.52; 95% CI 2.79 to 4.45). Using multiple logistic regression, black ethnic origin, raised body mass index, present smoking, booking systolic blood pressure of 130 to 139 mm Hg, and diastolic blood pressure of 80 to 89 mm Hg, a previous history of preeclampsia or eclampsia and chronic renal disease were identified as risk factors for superimposed preeclampsia. Adverse maternal and perinatal outcomes occur in women with chronic hypertension; the prevalence of infants born small for gestational age and preterm is considerably higher than background rates, and is increased further in women with superimposed preeclampsia. Use of customized birthweight centiles provides more accurate determination of fetal growth restriction and highlights the need for greater fetal surveillance in these women. Paradoxically, smoking is an independent risk factor for superimposed preeclampsia in chronic hypertension, in contrast to the protective effect in low-risk pregnant women. (Hypertension. 2008;51:1002-1009.)

Key Words: hypertension ■ pregnancy ■ preeclampsia ■ maternal morbidity ■ fetal morbidity ■ risk factors

Preeclampsia is estimated to affect 8,370,000 women worldwide every year. In the UK, it complicates approximately 4% to 6% of all pregnancies (approximately 33,500 per annum) and remains a major cause of maternal, fetal, and neonatal morbidity and mortality, contributing a significant healthcare economic burden. The disease not only affects pregnancy outcome, but also predisposes mother and child to long-term health complications such as cardiovascular disease. Currently, chronic hypertension is estimated to complicate between 1 and 5 percent of pregnancies; however the increase in maternal age and obesity and the changing ethnic profile of women in their reproductive years is likely to increase prevalence as these factors all impact on the hypertensive disease process. A small number of studies, mostly retrospective and from women investigated 1 to 2 decades ago, have documented the increased risk of adverse maternal and perinatal outcomes in pregnant women with chronic hypertension, but high quality recent prospective data are sparse. Information from contemporaneous cohorts is needed to provide an evidence base for the management of affected pregnant women and to inform future research.

Our group recently undertook a large prospective intervention study in women at increased risk of preeclampsia, for which chronic hypertension was an entry criterion. This trial has provided the largest cohort of women yet studied, with accurate prospectively collected outcome data, to report outcome of pregnancies complicated by chronic hypertension. The purpose of this study was to validate pregnancy outcome in women with chronic hypertension and to identify risk factors for superimposed preeclampsia.

Methods

The study population consisted of 861 women with chronic hypertension recruited from 25 hospitals in the United Kingdom and 1 hospital in the Netherlands between August 2003 and June 2005 into the Vitamins in Preeclampsia (VIP) trial, a randomized trial of antioxidant supplementation to prevent preeclampsia in pregnant women at increased risk. The South East Multi Ethics Research Committee approved the study (number 00/01/027). The study was registered as an International Standard Randomized Controlled Trial.
Table 1. Demographic, Pregnancy, and Management Characteristics of 822 Women With Chronic Hypertension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chronic Hypertensive Women (n=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y mean (SD)</td>
<td>32.9 (5.02)</td>
</tr>
<tr>
<td>Gestational age at enrollment, weeks mean (SD)</td>
<td>18.3 (2.53)</td>
</tr>
<tr>
<td>Booking body mass index, kg/m² median (IQR)</td>
<td>29.7 (25.2 to 35.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>198 (24%)</td>
</tr>
<tr>
<td>25 to 30</td>
<td>223 (27%)</td>
</tr>
<tr>
<td>30 to 35</td>
<td>188 (23%)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>213 (26%)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>304 (37%)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>518 (63%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>651 (79%)</td>
</tr>
<tr>
<td>Black</td>
<td>117 (14%)</td>
</tr>
<tr>
<td>Asian</td>
<td>37 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>547 (67%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>68 (8%)</td>
</tr>
<tr>
<td>Stopped before present pregnancy</td>
<td>153 (19%)</td>
</tr>
<tr>
<td>Stopped during present pregnancy</td>
<td>54 (7%)</td>
</tr>
<tr>
<td>Maternal diastolic blood pressure at enrollment, mm Hg</td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>275 (34%)</td>
</tr>
<tr>
<td>80 to 89</td>
<td>316 (38%)</td>
</tr>
<tr>
<td>≥90</td>
<td>231 (28%)</td>
</tr>
<tr>
<td>Maternal systolic blood pressure at enrollment, mm Hg</td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>335 (41%)</td>
</tr>
<tr>
<td>130 to 139</td>
<td>219 (27%)</td>
</tr>
<tr>
<td>≥140</td>
<td>268 (32%)</td>
</tr>
<tr>
<td>Dipstick proteinuria</td>
<td></td>
</tr>
<tr>
<td>Normal/trace</td>
<td>748 (91%)</td>
</tr>
<tr>
<td>+</td>
<td>39 (5%)</td>
</tr>
<tr>
<td>≥++</td>
<td>35 (4%)</td>
</tr>
<tr>
<td>Additional risk factors at enrollment (may be multiple)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>438 (53%)</td>
</tr>
<tr>
<td>Previous preeclampsia/HELLP/eclampsia</td>
<td>169 (21%)</td>
</tr>
<tr>
<td>Body mass index&gt;30 kg/m² in first pregnancy</td>
<td>154 (19%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (5%)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>35 (4%)</td>
</tr>
<tr>
<td>Abnormal uterine artery Doppler at 18 to 22 weeks</td>
<td>24 (3%)</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>9 (1%)</td>
</tr>
<tr>
<td>Medication at enrollment</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>304 (37%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>Current antihypertensive use</td>
<td>349 (43%)</td>
</tr>
<tr>
<td>Previous antihypertensive use</td>
<td>445 (54%)</td>
</tr>
</tbody>
</table>

Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chronic Hypertensive Women (n=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent additional medication after enrollment</td>
<td></td>
</tr>
<tr>
<td>Oral antihypertensive use</td>
<td>198 (24%)</td>
</tr>
<tr>
<td>Parenteral antihypertensive use</td>
<td>36 (4%)</td>
</tr>
<tr>
<td>Magnesium sulfate use</td>
<td>37 (5%)</td>
</tr>
</tbody>
</table>

number ISRCTN 62368611. Participants were enrolled into the study if they had 1 or more of 8 clinical risk factors for preeclampsia at a gestational age of 14<sup>th</sup> to 21<sup>st</sup> weeks after providing informed consent.

Of the 2404 women in total who participated, 861 were randomized with chronic hypertension as the entry criterion; of these 435 women were assigned to receive vitamin C (1000 mg) and vitamin E (400 IU) whereas 426 women were assigned to receive placebo daily until delivery. Thirty women with twin or triplet pregnancies were excluded because of the difficulties that multiple pregnancy presents as a confounding variable in the analysis of small for gestational age babies. Nine other women were also excluded because complete maternal and neonatal outcome datasets were missing. Personal and demographic data for the 822 women studied were obtained at the booking visit. Information on pregnancy outcome, complications, mode of delivery, delivery complications, birth weight, neonatal outcome, and length of maternal and neonatal stay in hospital were routinely recorded onto a customized study-specific internet-based database (MedSciNet). All data were collected by dedicated, trained, research midwives, with internal quality assurance, and checked independently by the clinical trials manager.

Chronic hypertension was defined as a diastolic blood pressure reading of 90 mm Hg or above (Korotkoff phase 5) at first or booking visit before the 20th week of gestation, or essential hypertension requiring medication, currently or previously. Superimposed preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. In this population all women were previously hypertensive, and therefore superimposed preeclampsia was defined by the new development of proteinuria. We defined proteinuria as excretion of 300 mg protein or more over 24 h or 2 readings of 2+ or more on dipstick analysis of midstream urine (MSU)/catheter specimen of urine (CSU) if 24-hour collection result was not available. For women with preexisting proteinuria, the diagnosis of preeclampsia was based on identification of clinical or biochemical markers or at least 1 additional feature of preeclampsia—eg, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, eclampsia. For these women, the trial management team reviewed each case of hypertensive pregnancy, and diagnosis was confirmed by 2 senior clinical staff acting independently.

Birthweights were recorded and centiles calculated by customized birthweight centile charts (Gestation Related Optimal Weight [GROW]); small for gestational age (SGA) was defined as being less than the 10th centile. We also identified the following prespecified maternal and neonatal outcomes: early onset preeclampsia (diagnosis at or before 34 weeks gestation), preterm birth (<34 and <37 weeks gestation, both spontaneous and iatrogenic), mode of delivery, eclampsia, HELLP syndrome, death of the child (intrauterine or neonatal deaths by 28 days), admission to neonatal unit (NNU) or the special care baby unit (SCBU) for more than 7 days, low birthweight (<2.5 kg), and intraventricular hemorrhage. Length of maternal inpatient stay was recorded.

Nonfasting venous samples were obtained from 515 women with chronic hypertension at trial entry before randomization (mean gestational age at sampling 18<sup>th</sup> to 22<sup>nd</sup>). Plasma and serum were stored in aliquots at −80°C. Vitamin C, vitamin E (α-tocopherol), and cholesterol were assayed as previously described. Uric acid concentrations were determined by reverse phase high-pressure liquid chromatography (HPLC). Nonfasting plasma triglycerides were measured with an enzymatic colorimetric test (UNIMATE 5
Table 2. Maternal and Neonatal Outcomes of Women With Superimposed Preeclampsia Versus Women With No Preeclampsia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Superimposed Preeclampsia (n=180)</th>
<th>No Preeclampsia (n=642)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset preeclampsia</td>
<td>79 (44%)</td>
<td>94 (15%)</td>
<td>3.52 (2.79 to 4.45)</td>
</tr>
<tr>
<td>Preterm birth ≤37 weeks</td>
<td>93 (51%)</td>
<td>94 (15%)</td>
<td>3.52 (2.79 to 4.45)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>2 (1%)</td>
<td>32 (5%)</td>
<td>0.22 (0.53 to 0.92)</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>91 (50%)</td>
<td>62 (10%)</td>
<td>5.23 (3.96 to 6.90)</td>
</tr>
<tr>
<td>Preterm birth ≤34 weeks</td>
<td>42 (23%)</td>
<td>48 (7%)</td>
<td>3.12 (2.13 to 4.56)</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>43 (24%)</td>
<td>291 (45%)</td>
<td>0.52 (0.40 to 0.69)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>11 (6%)</td>
<td>67 (10%)</td>
<td>0.58 (0.32 to 1.08)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>126 (70%)</td>
<td>284 (44%)</td>
<td>1.58 (1.39 to 1.80)</td>
</tr>
<tr>
<td>Elective</td>
<td>89 (49%)</td>
<td>170 (27%)</td>
<td>1.87 (1.53 to 2.27)</td>
</tr>
<tr>
<td>Emergency</td>
<td>37 (21%)</td>
<td>114 (18%)</td>
<td>1.15 (0.83 to 1.61)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>HELLP</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Total inpatient stay (days; mean, SD)</td>
<td>12.7 (9.3)</td>
<td>5.4 (7.0)</td>
<td>7.2 (5.8 to 8.7)*</td>
</tr>
<tr>
<td>Antenatal</td>
<td>7.3 (7.9)</td>
<td>2.3 (5.9)</td>
<td>5.0 (3.7 to 6.2)*</td>
</tr>
<tr>
<td>Postnatal</td>
<td>5.5 (3.7)</td>
<td>3.2 (2.6)</td>
<td>2.3 (1.7 to 2.8)*</td>
</tr>
<tr>
<td><strong>Neonatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal deaths</td>
<td>5 (3%)</td>
<td>12 (2%)</td>
<td>1.11 (0.41 to 3.00)</td>
</tr>
<tr>
<td>Deaths after delivery</td>
<td>2 (1%)</td>
<td>5 (1%)</td>
<td>1.42 (0.28 to 7.29)</td>
</tr>
<tr>
<td>Admission to NNU/SCBU</td>
<td>64 (35%)</td>
<td>77 (12%)</td>
<td>2.98 (2.24 to 3.98)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>6 (3%)</td>
<td>3 (0.5%)</td>
<td>7.13 (1.80 to 28.2)</td>
</tr>
<tr>
<td>&lt;5th birthweight centile</td>
<td>75 (42%)</td>
<td>91 (14%)</td>
<td>2.94 (2.27 to 3.80)</td>
</tr>
<tr>
<td>&lt;10th birthweight centile</td>
<td>87 (48%)</td>
<td>137 (21%)</td>
<td>2.30 (1.85 to 2.84)</td>
</tr>
<tr>
<td>&gt;95th birthweight centile</td>
<td>15 (8%)</td>
<td>61 (9%)</td>
<td>0.88 (0.51 to 1.50)</td>
</tr>
<tr>
<td>Low birthweight (&lt;2.5 kg)</td>
<td>79 (44%)</td>
<td>85 (13%)</td>
<td>3.31 (2.56 to 4.29)</td>
</tr>
<tr>
<td>Macrosomia (≥4.0 kg)</td>
<td>7 (3.7%)</td>
<td>85 (13%)</td>
<td>0.36 (0.16 to 0.81)</td>
</tr>
</tbody>
</table>

*For economic data, differences in the mean are given with confidence intervals estimated by bootstrap with 10,000 replications.

TRIG, Roche/BiC). High-density lipoprotein (HDL) cholesterol was determined by detergent-based isolation and enzyme-linked colorimetric detection (DIRECT HDL CHOLESTEROL, RANDOX Laboratories Co). Low-density lipoprotein (LDL) cholesterol was estimated by calculation from triglycerides and HDL cholesterol. Malondialdehyde (MDA), a marker of lipid peroxidation, was measured by HPLC-based thiobarbituric acid tests.10

As reported in the Vitamins in Preeclampsia trial,6 across all participants there was an increase in low birth weight (though not small for gestational age infants) in the antioxidant group. As reported previously in the antioxidant supplementation trial,6 supplementation had no impact on birth weight in pregnancies complicated by chronic hypertension (including preeclampsia, delivery of a small for gestational age infant or preterm birth [96/419 [22.9%] in treatment group versus 91/103 [22.6%] in placebo arm; RR 1.01 [95% CC 0.79 to 1.31], P=0.91]). Data from both treatment and placebo groups were therefore combined.

All statistical analyses were performed using the statistical software package Stata, version 9.2 (StataCorp LP). Univariate statistics were used to assess the differences in demographic, maternal, and neonatal outcomes and laboratory parameters in the whole cohort and between the 2 groups of women with chronic hypertension. These are reported as n (%), mean (standard deviation [SD]), or median (interquartile range [IQR]). Age, parity, race, body mass index, booking systolic, and diastolic blood pressures were divided into categories and comparisons made with maternal and perinatal outcomes using χ² test. Continuous data were compared with a 2-tailed Student t test. Risk ratios with 95% confidence interval were calculated to determine the relationship between the primary outcome and maternal and neonatal end points. As differences in the arithmetic mean of economic data are generally considered important, bootstrapping was used to develop confidence intervals for differences in the arithmetic mean for indices of use of healthcare resources (antenatal and postnatal inpatient stay). Risk factors for continuous outcome were analyzed using linear regression with robust standard errors, and for binary outcome using logistic regression expressed as odds ratio with 95% confidence interval as appropriate. Estimates were adjusted for age, maternal body mass index, ethnicity, smoking, and maternal booking diastolic and systolic blood pressure (except estimates for systolic BP were not adjusted for diastolic BP and vice versa). A shorter list of significant adjustments was also used: body mass index, ethnic origin (black), present smoking, systolic BP and diastolic BP at booking, and
present antihypertensive therapy. Where data are reported as median (IQR), differences in the median were estimated using quantile regression.

Results

In women with chronic hypertension who participated in this study, 22% developed superimposed preeclampsia; nearly half of these (44%) had early-onset disease before 34 weeks gestation.

Table 1 describes the demographic, pregnancy, and management characteristics of 822 women with chronic hypertension who participated in the study. Mean diastolic blood pressure was 82 mm Hg (range 50 to 121 mm Hg) with 42% (n=352) of women at enrollment being on antihypertensive therapy. Of the participants studied, 47% (n=388) had more than one risk factor. There was no difference in the occurrence of preeclampsia among those women taking aspirin (72/303 [23.8%]) and those not taking aspirin (108/519 [20.8%]; risk ratio 1.14 [95% CI 0.88 to 1.48]; P=0.32).

Table 2 compares the maternal and neonatal outcomes between 180 women with superimposed preeclampsia and 642 without. There were no significant differences between these groups in terms of age, maternal body weight, or parity. Two maternal deaths occurred among the women; one woman committed suicide 5 days postpartum while the other woman died as a result of an infection 6 months postpartum.

Table 3 reports the prevalence of 3 major adverse outcomes, superimposed preeclampsia, <10th birthweight centile and preterm delivery <37 weeks gestation, stratified by baseline characteristics; the odds ratios for the development of superimposed preeclampsia for each of the risk factors are reported in Table 4. Age >40 yr, black ethnic origin, booking systolic blood pressure >140 mm Hg, and booking diastolic blood pressure >90 mm Hg were associated with small for gestational age babies and preterm delivery in women with chronic hypertension.

The following risk factors for preeclampsia were identified using logistic regression: raised body mass index, black

Table 3. Prevalence of Adverse Perinatal Outcomes Stratified by Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Preeclampsia</th>
<th>Birthweight Centile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10th</td>
<td>Preterm Delivery</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>&lt;37 Weeks</td>
</tr>
<tr>
<td>&lt;30 (n=187)</td>
<td>41 (22%)</td>
<td>36 (19.3%)</td>
</tr>
<tr>
<td>30 to 40 (n=565)</td>
<td>126 (22.3%)</td>
<td>119 (21.1%)</td>
</tr>
<tr>
<td>&gt;40 (n=70)</td>
<td>14 (20.0%)</td>
<td>19 (26.8%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (n=198)</td>
<td>32 (16.1%)</td>
<td>44 (22.2%)</td>
</tr>
<tr>
<td>25 to 30 (n=223)</td>
<td>56 (25.1%)</td>
<td>49 (21.9%)</td>
</tr>
<tr>
<td>30 to 35 (n=188)</td>
<td>40 (21.3%)</td>
<td>32 (17.0%)</td>
</tr>
<tr>
<td>&gt;35 (n=213)</td>
<td>58 (27.2%)</td>
<td>41 (19.2%)</td>
</tr>
<tr>
<td>Nulliparity (n=304)</td>
<td>67 (22.0%)</td>
<td>80 (26.3%)</td>
</tr>
<tr>
<td>Multiparity (n=518)</td>
<td>113 (21.8%)</td>
<td>142 (27.4%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (n=651)</td>
<td>126 (19.3%)</td>
<td>109 (16.7%)</td>
</tr>
<tr>
<td>Black (n=117)</td>
<td>40 (34.2%)</td>
<td>40 (34.1%)</td>
</tr>
<tr>
<td>Asian (n=37)</td>
<td>10 (27.0%)</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td>Other (n=17)</td>
<td>5 (29.4%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (n=547)</td>
<td>116 (21.2%)</td>
<td>151 (20.3%)</td>
</tr>
<tr>
<td>Current (n=68)</td>
<td>20 (29.4%)</td>
<td>21 (23.5%)</td>
</tr>
<tr>
<td>Stopped before present pregnancy (n=153)</td>
<td>30 (19.6%)</td>
<td>34 (18.8%)</td>
</tr>
<tr>
<td>Stopped during present pregnancy (n=54)</td>
<td>14 (30.0%)</td>
<td>16 (29.6%)</td>
</tr>
<tr>
<td>Systolic blood pressure at booking, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130 (n=335)</td>
<td>49 (14.6%)</td>
<td>47 (14.0%)</td>
</tr>
<tr>
<td>130 to 139 (n=219)</td>
<td>69 (31.5%)</td>
<td>52 (23.7%)</td>
</tr>
<tr>
<td>&gt;140 (n=268)</td>
<td>62 (23.1%)</td>
<td>67 (25.0%)</td>
</tr>
<tr>
<td>Diastolic blood pressure at booking, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80 (n=275)</td>
<td>42 (15.3%)</td>
<td>39 (14.2%)</td>
</tr>
<tr>
<td>80 to 89 (n=316)</td>
<td>82 (30.0%)</td>
<td>62 (19.6%)</td>
</tr>
<tr>
<td>&gt;90 (n=231)</td>
<td>56 (24.3%)</td>
<td>65 (28.1%)</td>
</tr>
</tbody>
</table>
ethnicity, present smoking, booking systolic blood pressure of 130 to 139 mm Hg, booking diastolic blood pressure of 80 to 90 mm Hg, and present antihypertensive use (Table 4). A previous history of preeclampsia, HELLP, or eclampsia and chronic renal disease as well as the presence of 1 or more additional risk factors in addition to chronic hypertension were significantly associated with the development of pre-eclampsia after adjusting for differences in age, parity, race, smoking, body mass index, as well as booking systolic and diastolic blood pressures (Table 5).

Plasma vitamin C was 9.2 H9262mol/L lower (95% CI 3.75 to 14.82) at enrollment in those women who developed superimposed preeclampsia compared to those who did not. The occurrence of preeclampsia decreased as the plasma concentration of vitamin C increased, from 29% (37/129) in the lowest quartile (<52 μmol/L) to 14% (18/129) in the highest quartile (>86.8 μmol/L); odds ratio 0.41 (95% CI 0.22 to 0.76; P=0.001 by logistic regression, testing for trend). There were no significant differences in any other analyte measured (Table 6).

### Discussion

This is the largest prospective study of pregnancy outcome in women with chronic hypertension to be reported to date. We have documented a significant risk (22%) of superimposed preeclampsia, similar to that reported by 3 previous, but smaller, observational studies of women with chronic hypertension from New Zealand (17%),4 Canada (21%)3 and a study of 763 women in the United States (25%).5 Whether or not these women develop superimposed preeclampsia, adverse maternal and perinatal outcomes are increased, including clinically relevant indices such as fetal growth restriction (48% and 21% respectively), preterm birth (51% and 15%) and Caesarean section (70% and 44%). Those reflecting the

| Table 4. Effect of Baseline Characteristics on the Development of Superimposed Preeclampsia |
|-----------------------------------------------|---------------|---------------|-----------------------------|
| Risk Category                           | Unadjusted Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* | Adjusted Odds Ratio (95% CI)† (Significant Predictors Only) |
| Age, y                                   |                                      |                            |                             |
| <30                                      | 1.00 (reference)                     |                             |                             |
| 30 to 40                                 | 1.07 (0.69 to 1.65)                  | 0.95 (0.01 to 1.50)         |                             |
| >40                                      | 0.92 (0.59 to 1.44)                  | 0.76 (0.47 to 1.24)         |                             |
| Nulliparity                              | 1.00 (reference)                     |                             |                             |
| Multiparity                              | 0.98 (0.70 to 1.39)                  | 0.84 (0.58 to 1.21)         |                             |
| Body mass index, kg/m²                   |                                      |                            |                             |
| <25                                      | 1.00 (reference)                     |                             |                             |
| 25 to 30                                 | 1.80 (1.10 to 2.94)                  | 1.70 (1.02 to 2.82)         | 1.69 (1.02 to 2.80)         |
| 30 to 35                                 | 1.45 (0.86 to 2.44)                  | 1.29 (0.75 to 2.24)         | 1.27 (0.74 to 2.19)         |
| >35                                      | 1.78 (1.09 to 2.92)                  | 1.61 (0.96 to 2.69)         | 1.59 (0.96 to 2.65)         |
| Ethnic origin                            |                                      |                            |                             |
| White                                    | 1.00 (reference)                     |                             |                             |
| Black                                    | 2.08 (1.35 to 3.20)                  | 2.49 (1.54 to 4.04)         | 2.31 (1.47 to 3.63)         |
| Asian                                    | 1.54 (0.73 to 3.27)                  | 1.59 (0.71 to 3.55)         |                             |
| Other                                    | 1.73 (0.60 to 5.01)                  | 1.45 (0.47 to 4.47)         |                             |
| Smoking                                  |                                      |                            |                             |
| Never                                    | 1.00 (reference)                     |                             |                             |
| Current                                  | 1.59 (0.91 to 2.80)                  | 1.87 (1.02 to 3.40)         | 1.79 (1.01 to 3.18)         |
| Stopped before present pregnancy         | 0.94 (0.60 to 1.47)                  | 1.01 (0.63 to 1.62)         |                             |
| Stopped during present pregnancy         | 1.31 (0.69 to 2.80)                  | 1.43 (0.73 to 2.82)         |                             |
| Systolic blood pressure at booking, mm Hg |                                      |                            |                             |
| <130                                     | 1.00 (reference)                     |                             |                             |
| 130 to 139                               | 2.68 (1.71 to 4.19)                  | 2.80 (1.82 to 4.30)         | 2.84 (1.85 to 4.35)         |
| >140                                     | 1.75 (1.16 to 2.66)                  | 1.70 (1.11 to 2.61)         | 1.70 (1.11 to 2.61)         |
| Diastolic blood pressure at booking, mm Hg |                                      |                            |                             |
| <80                                      | 1.00 (reference)                     |                             |                             |
| 80 to 89                                 | 1.94 (1.28 to 2.94)                  | 2.04 (1.33 to 3.13)         | 1.73 (1.12 to 2.69)         |
| >90                                      | 1.77 (1.13 to 2.77)                  | 1.65 (1.04 to 2.61)         | 1.30 (0.77 to 2.18)         |
| Current antihypertensive use              | 1.43 (1.03 to 2.00)                  | 1.34 (0.94 to 1.91)         | 1.31 (0.92 to 1.85)         |

*Estimates adjusted for age, parity, body mass index, ethnic origin, smoking, systolic BP, and diastolic BP at booking and current antihypertensive therapy (except systolic BP estimates not adjusted for diastolic BP and vice versa).

†Estimates adjusted for body mass index, ethnic origin (black), current smoking, systolic BP, and diastolic BP at booking and current antihypertensive therapy (except systolic BP estimates not adjusted for diastolic BP vice versa).
Body mass index (H11022) kg/m² in first pregnancy
HELLP/eclampsia
Previous preeclampsia/

customized birthweight centiles to accurately assess fetal
pregnant women with chronic hypertension to have used
extrapolated to the wider population.

index, and additional risk factors, enabling these results to be
diverse spectrum with respect to age, ethnicity, body mass
provides contemporaneous data and in-depth analysis of
ten presents a dilemma for accurate diagnosis. Our study
hypertension, gestational hypertension and preeclampsia of-
particularly in this scenario where overlap between chronic

discharge coding, known to be fraught with inaccuracies,11

Previous reports have often relied on hospital event or
discharge coding, known to be fraught with inaccuracies,11
particularly in this scenario where overlap between chronic
hypertension, gestational hypertension and preeclampsia of-

Because the rate of smoking and the degree of protein-
uria, both associated with fetal growth restriction are similar
across the different studies, our data suggest that the use of
customized birthweight centiles yields a greater detection rate
of an important marker of adverse perinatal outcome. In a
population based cohort study of over 326 000 women, the
use of customized birthweight centiles has been shown to
increase identification of fetuses at risk of stillbirth, neonatal
death, and Apgar score under 4 at 5 min.13 In a recent study,
introduction of a new classification system for stillbirths
using customized birthweight centiles led to identification of
fetal growth restriction as the most common coexisting
complication (43%) whereas 58% of those stillbirths previ-
ously labeled as “unexplained” by the older Wigglesworth
system14 (routinely used for the purpose of national statistics)
were shown to have fetal growth restriction.12 Although
the presence of additional risk factors among 47% of the women
in our study may have made some contribution to the greater
prevalence of infants small for gestational age compared with
previous reports, it is unlikely to explain the entire difference
as chronic hypertension was a sole entry criterion to the
study. Other comorbidities were therefore coincidental, as
they would have been among women recruited to previous
studies, and are likely to reflect the wider population of
women with chronic hypertension. However, in contempo-
rary developed societies it should be recognized that obesity
is likely to be an increasingly common coexisting indepen-
dent risk factor for preeclampsia. The largest previous study
in women with chronic hypertension5 did not report body
growth restriction. Adjusting birthweight centiles for the
fetus’s sex and maternal height and weight, parity, and ethnic
origin enables a distinction to be drawn between an infant
being constitutionally and pathologically small for gestational
age. On this basis a newborn infant less than the 10th

customized birthweight centile can be considered to be
growth restricted.12 Delivery of an infant less than 10th

customized birthweight centile complicated nearly half
(48.3%) of those women with superimposed preeclampsia
and one fifth (21.0%) of those without preeclampsia. These
figures are markedly higher than those reported in the only
other large study (763 women with chronic hypertension)
from a United States population (13% and 11%, respective-
ly)4 and earlier smaller studies from New Zealand (19% and
11%, respectively)4 and Canada (15% and 11%, respective-
ly).3

Table 5. Effect of Major Risk Factors in Addition to Chronic
Hypertension on the Development of Superimposed
Preeclampsia

<table>
<thead>
<tr>
<th>Additional Major Risk Factor</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous preeclampsia/HELLP</td>
<td>1.69 (1.15 to 2.47)</td>
<td>1.95 (1.25 to 3.04)</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m² in first pregnancy</td>
<td>1.07 (0.71 to 1.63)</td>
<td>1.06 (0.52 to 2.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.45 (0.73 to 2.90)</td>
<td>1.50 (0.73 to 3.11)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>1.92 (0.93 to 3.94)</td>
<td>2.17 (1.00 to 4.66)</td>
</tr>
<tr>
<td>Abnormal uterine artery Doppler at 18 to 22 weeks</td>
<td>1.82 (0.76 to 4.32)</td>
<td>1.46 (0.58 to 3.66)</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>1.02 (0.21 to 4.95)</td>
<td>1.11 (0.21 to 5.85)</td>
</tr>
<tr>
<td>Chronic hypertension with 1 additional risk factor</td>
<td>1.50 (1.06 to 2.12)</td>
<td>1.55 (1.06 to 2.28)</td>
</tr>
<tr>
<td>Chronic hypertension with 2 additional risk factors</td>
<td>2.74 (1.45 to 5.16)</td>
<td>2.97 (1.50 to 5.87)</td>
</tr>
</tbody>
</table>

*Estimates adjusted for age, parity, body mass index, ethnic origin, smoking, systolic BP, and diastolic BP at booking and current antihypertensive therapy by multiple logistic regression.

The economic burden of disease including maternal inpatient stay (12.7 days and 5.4 days) and neonatal unit admission (35% and 12%) are also raised.

This study adds significantly to the literature as the analysis was undertaken on a large cohort, and used a prospectively validated diagnosis of chronic hypertension, customized growth centiles, and a rigorous definition of superimposed preeclampsia, which included confirmation of the diagnosis by senior clinical staff acting independently.

Previous reports have often relied on hospital event or discharge coding, known to be fraught with inaccuracies,11 particularly in this scenario where overlap between chronic hypertension, gestational hypertension and preeclampsia often presents a dilemma for accurate diagnosis. Our study provides contemporaneous data and in-depth analysis of women from a large number of centers within the UK with a diverse spectrum with respect to age, ethnicity, body mass index, and additional risk factors, enabling these results to be extrapolated to the wider population.

This study is the first among those reporting outcomes in pregnant women with chronic hypertension to have used customized birthweight centiles to accurately assess fetal
deliveries (48.3%) of those women with superimposed preeclampsia
and one fifth (21.0%) of those without preeclampsia. These
figures are markedly higher than those reported in the only
other large study (763 women with chronic hypertension)
from a United States population (13% and 11%, respective-
ly)4 and earlier smaller studies from New Zealand (19% and
11%, respectively)4 and Canada (15% and 11%, respective-
ly).3

Table 6. Blood Parameters Measured at Enrollment

<table>
<thead>
<tr>
<th>Blood Parameter</th>
<th>Superimposed Preeclampsia (n=114)</th>
<th>No Preeclampsia (n=403)</th>
<th>Difference: 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C, μmol/L</td>
<td>61.7 (25.1)</td>
<td>71.1 (27.3)</td>
<td>−9.3 (−14.7 to −4.0)</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>199.4 (64.3)</td>
<td>186.2 (51.5)</td>
<td>13.2 (0.2 to 26.1)</td>
</tr>
<tr>
<td>Malondialdehyde, nmol/L</td>
<td>2.12 (0.53)</td>
<td>2.01 (0.48)</td>
<td>0.11 (−0.00 to 0.22)</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.61 (0.74)</td>
<td>1.42 (0.71)</td>
<td>0.19 (0.04 to 0.34)</td>
</tr>
<tr>
<td>α-tocopherol, μmol/L</td>
<td>29.4 (9.5)</td>
<td>29.7 (8.3)</td>
<td>−0.3 (−2.2 to 1.6)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.10 (0.89)</td>
<td>5.21 (0.91)</td>
<td>−0.10 (−0.29 to 0.08)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.85 (0.88)</td>
<td>3.01 (0.87)</td>
<td>−0.17 (−0.35 to 0.02)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.45 (0.16)</td>
<td>1.49 (0.15)</td>
<td>−0.03 (−0.06 to 0.00)</td>
</tr>
</tbody>
</table>

*All values are mean (SD).
mass index or rates of obesity, but in the present study 1 in 2 women were clinically obese. The odds ratio for the development of preeclampsia increased even in overweight women (BMI 25 to 30); lack of additional effect with further increases in BMI may reflect fewer numbers of women in these groups. The clinical implications for the remarkably high incidence of growth restriction are significant and suggest that surveillance for fetal growth restriction with regular ultrasound assessment is an essential component of the antenatal care for all women with chronic hypertension, dispelling the widely held opinion that the disease is relatively innocent from a fetal perspective, particularly in the absence of superimposed preeclampsia.

Our study also provides novel data on the increased risk of superimposed preeclampsia in women with chronic hypertension who continue to smoke in pregnancy. This is particularly striking given the paradoxical decreased relative risk of preeclampsia among smokers; a recent systematic review reported a relative risk for preeclampsia of 0.68 (95% CI 0.67 to 0.69) in a meta-analysis of data from over 800,000 women in cohort studies. The possible biological mechanisms for this finding have been widely discussed and include the selective inhibition of thromboxane A2, stimulation of nitric oxide production by nicotine, vasodilatory effects of carbon monoxide, and most recently, a decrease in soluble flt-1. Present smoking during pregnancy was associated with a near doubling of the adjusted odds ratio for preeclampsia in our study. This increased risk is not explicable as an idiosyncratic feature of our study population; the odds ratio for the effect of smoking on preeclampsia for the women without chronic hypertension who participated in the Vitamins In Preeclampsia study was 0.67 (95% CI 0.37 to 1.20), similar to that in the systematic review. It is plausible that the maternal microvascular damage and endothelial dysfunction associated with chronic hypertension may switch the effect of smoking from protective to harmful. Previous studies of chronic hypertensive pregnant women have not reported the risk of preeclampsia stratified by smoking status; our findings have important clinical implications particularly for general physicians involved in the care of these women who should put added emphasis on smoking cessation guidance.

In addition to identifying smoking as a novel risk factor, use of logistic regression has highlighted the other predictors of greatest importance for this group of pregnant women with chronic hypertension. Black ethnicity, the presence of additional clinical risk factors, and to a lesser degree raised body mass index, all increase the adjusted odds ratio for the development of preeclampsia. Previous studies have yielded conflicting data on the impact of ethnicity; one study reported an increased risk of superimposed preeclampsia in black women compared to white (32% versus 15%), whereas a more recent study showed no difference (25% versus 26%). A recent systematic review and meta-analysis of risk factors for preeclampsia confirmed the increased risk conferred by additional clinical risk factors (including previous preeclampsia) and raised body mass index reported here.

It was surprising that the effect of a booking diastolic blood pressure of >90 mm Hg on the risk of subsequent preeclampsia was not substantially greater than that of a diastolic blood pressure of 80 to 89 mm Hg, and similarly for systolic blood pressure >140 mm Hg as compared to 130 to 139 mm Hg, even after correction for use of antihypertensive drugs at booking. One possible explanation for this unexpected result would be that this group includes women with treated long-standing chronic hypertension, whereas those with higher booking blood pressures represent women with newly diagnosed hypertension in whom maternal vascular damage (and the subsequent risk of superimposed preeclampsia) is less marked. However, as the confidence intervals for the subgroups overlap, there may be no real difference.

It is also of note that age and parity had no significant effect on the subsequent risk of superimposed preeclampsia in our study cohort; a similar lack of effect of maternal age in women with chronic hypertension was found by Sibai and colleagues. This is in contrast to the recent systematic review of unselected women in which an adjusted odds ratio of 2.91 (1.28 to 6.61) for preeclampsia was found for nulliparity and which quotes a nationwide US study suggesting that the risk of preeclampsia increases by 30% for every additional year of age past 34. The clinical implications of this for pregnant women with chronic hypertension are that multiparity or lower maternal age are not protective, and therefore that heightened surveillance for superimposed preeclampsia is also appropriate for these women.

Potential issues include the use of both arms of the original intervention trial for this dataset. This followed the finding that there was no significant difference in the occurrence of preeclampsia between women with chronic hypertension in the active arm receiving 1000 mg vitamin C and 400 IU vitamin E (100/435, 23%) and those in the placebo arm (94/422, 22%). and therefore this strategy is justified. Similarly no significant difference was found in the occurrence of low birthweight babies or small for gestational age infants between the 2 arms. Likewise, Sibai and colleagues included both arms of the trial in the next largest series of chronic hypertensive pregnant women who participated in an intervention study assessing aspirin.

None of the biochemical parameters measured at randomization was useful as a predictor of outcome. It is unlikely that the small statistically different values of vitamin C at enrollment (before active treatment) would have any clinically useful prognostic role in prediction given the magnitude of the absolute difference. There is a need for predictive biomarkers for preeclampsia in women with chronic hypertension that would allow stratification of risk and surveillance and potential targeting of therapeutic interventions to ameliorate the disease process.

**Perspectives**

This study represents the most comprehensive and contemporaneous prospective dataset of pregnant women with chronic hypertension and documents the clinically significant occurrence of adverse maternal and perinatal outcomes in this group. Using customized birthweight centiles, we have highlighted the high prevalence of fetal growth restriction, suggesting that customized birthweight centiles are needed in clinical practice. The novel finding of the increased risk of superimposed preeclampsia in chronic hypertensive women...
who smoke has important implications for advice given by obstetricians and general physicians. All doctors involved in the care of these women must appreciate the increased risk, not only for future cardiovascular disease, but also for perinatal risk, particularly fetal growth restriction. Regular maternal supervision for superimposed preeclampsia is justified; intensive fetal surveillance is not routinely used by all, and is required.

Acknowledgments

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Disclosures


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