Manifestations of Metabolic Syndrome After Hypertensive Pregnancy

Anneli Pouta, Anna-Liisa Hartikainen, Ulla Sovio, Mika Gissler, Jaana Laitinen, Mark I. McCarthy, Aimo Ruokonen, Paul Elliott, Marjo-Riitta Järvelin

Abstract—Small follow-up studies of hospital-based series indicate women with preeclampsia have an increased risk of insulin resistance postpartum. However, long-term data are lacking among women with gestational hypertension without proteinuria. Using a general population-based sample of 5889 women from Northern Finland followed longitudinally since birth in 1966, we examined these associations and the influence of the subject’s own birth weight and gestational age on this relationship. At age 31, blood pressure was measured and blood samples collected from 2678 women, of which 1463 women had had at least 1 singleton pregnancy. Of these, 45 had been hospitalized because of gestational hypertension and 49 because of preeclampsia. Women who had had either gestational hypertension or preeclampsia during their first pregnancy (average age 25 years) had increased blood pressure at 31 years compared with women with previous normotensive pregnancy, even after adjustment for body mass index (P<0.001 in gestational hypertension, P=0.023 in preeclampsia group). When compared with the whole female population, women with previous gestational hypertension at same age still had higher blood pressure, while this difference was weaker for women with previous preeclampsia. Women with gestational hypertension and preeclampsia also higher waist circumference, waist/hip ratio, and body mass index, as well as increased serum insulin levels and lower glucose/insulin ratio than women with previous normotensive pregnancy. The associations remained after adjustment for participant’s own birth weight or gestational age. Women born before gestational week 37 had a 2-fold risk for gestational hypertension in their first pregnancy (RR: 2.53; 95% CI: 1.0, 6.2). (Hypertension. 2004;43:1-7.)

Key Words: cohort studies ■ hypertension ■ low birth weight ■ insulin resistance ■ longitudinal studies ■ preeclampsia ■ pregnancy

The pathophysiology of de novo hypertension in pregnancy, ie, preeclampsia and transient gestational (non-proteinuric) hypertension, is poorly understood. There are some indications that insulin resistance may play a role. Five postpartum studies showed that women with a history of preeclampsia are more often hyperinsulinemic than those with normotensive pregnancies, although this has not been confirmed in all studies. These women may be at higher risk for cardiovascular diseases, but so far the study populations of the postpartum studies of insulin resistance were small and the follow-up periods short (<1 year), except 2 studies until postmenopause. To our knowledge, there are no previous long-term studies of insulin resistance in women with a history of gestational hypertension. Several studies also suggest that low birth weight is associated with increased cardiovascular disease risk in adults, and 2 indicate a positive association between own preterm birth/low birth weight and later preeclampsia, although data are lacking for women with gestational hypertension only.

In this population-based prospective study, we tested the a priori hypothesis that women with gestational hypertension or preeclampsia during their first pregnancy show an unfavorable lipid profile and hyperinsulinemia at age 31 years and that this association is modified by own birth weight.

Methods

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

All births in the 2 northernmost provinces of Finland with expected dates of delivery during 1966 were eligible for the Northern Finland 1966 Birth Cohort (NFBC 1966, coverage 96%); 5889 females were born alive, and 4074 women were invited to a follow-up in 1997 to 1998 (Figure 1). Of the female cohort consisting of 2678 eligible women with blood pressure (BP) measurement, blood samples, and written consent, 68% had had at least one delivery (Figure 1). To ascertain...
women with gestational hypertension or preeclampsia, we used 2 routes. First, data on their first pregnancies were obtained from the Medical Birth Register (MBR), which covers all deliveries in Finland from January 1, 1987 onward. Second, data on all hospital admissions from childhood until 1998 were collected from the Hospital Discharge Register (HDR). Women with one of the following diagnosis codes: 6423 to 6426, 6429, and O13-O16 (International Classification of Diseases ICD-9/10) were considered to have de novo hypertension during pregnancy. The MBR and HDR were cross-checked to trace all women with gestational hypertension with and without proteinuria for further hospital chart review (by A.P.) of all hypertensive cases (Figure 1). Preeclampsia was diagnosed if there was a BP of $140/90$ mm Hg, measured twice 6 or more hours apart, and consistent proteinuria of $300$ mg/d or more after gestational week 20 in a previously normotensive woman. The criteria for gestational hypertension were similar to preeclampsia, but these women had proteinuria $<300$ mg/d.

The final study population included 1463 women. The hypertensive group consisted of 94: 45 hospitalized because of gestational hypertension, 30 because of mild preeclampsia, and 19 because of severe preeclampsia. According to the MBR/HDR or on chart review during their first pregnancy, 1369 women had had no hypertensive disorder. These form the reference group (Figure 1). From the reference group, files of 63 randomly selected women were reviewed: none had preeclampsia but 2 had at least 2 BP measurements slightly above the criteria and 1 had chronic hypertension (untreated).

**Data Collection and Clinical Examination**

Socioeconomic position, maternal parity, own birth weight, length, and gestational age at birth were obtained from the NFBC database and data on the participant’s first delivery (index pregnancy) from the MBR and separately for women with hypertension, also from hospital charts.

Data on outcomes at age 31 were collected at clinical examination during 1997 to 1998. The average proportion of missing values was 1.5% in the hypertensive and 1.6% in the reference group. BP was measured twice with a sphygmomanometer in sitting position after 15 minutes rest. Blood was collected after an overnight fast (8:00 to 11:00 AM), and glucose and lipid samples were stored at 4°C and analyzed within 24 hours; serum insulin samples were stored at $-20^\circ$C and analyzed within 7 days of sampling.

**Statistical Analysis**

The association between own birth measures and risk of gestational hypertension and preeclampsia was explored graphically and using linear and polynomial logistic regression models. Risk ratios (RR) of gestational hypertension/preeclampsia were calculated for low birth weight using cut-off $<2750$ g because of low prevalence of birth...
TABLE 1. Women's Own Birth Measures in 1966 and Relative Risk (RR) For Later Gestational Hypertension (GH) and Preeclampsia (PE)

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Total N</th>
<th>GH %</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>PE %</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>GH and PE %</th>
<th>N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;31 gestational week</td>
<td>68</td>
<td>7.4</td>
<td>5</td>
<td>2.23 (1.0, 6.2)</td>
<td>4.4</td>
<td>3</td>
<td>1.34 (0.4, 4.2)</td>
<td>11.8</td>
<td>8</td>
<td>1.90 (1.0, 3.8)</td>
</tr>
<tr>
<td>≥31 gestational week</td>
<td>1341</td>
<td>2.9</td>
<td>39</td>
<td>1.00</td>
<td>3.3</td>
<td>44</td>
<td>1.00</td>
<td>6.2</td>
<td>83</td>
<td>1.00</td>
</tr>
<tr>
<td>Birth weight</td>
<td>&lt;2750 g</td>
<td>103</td>
<td>5.8</td>
<td>6</td>
<td>2.03 (0.9, 4.7)</td>
<td>5.8</td>
<td>6</td>
<td>1.84 (0.8, 4.2)</td>
<td>11.7</td>
<td>12</td>
</tr>
<tr>
<td>≥2750 g</td>
<td>1360</td>
<td>2.9</td>
<td>39</td>
<td>1.00</td>
<td>3.2</td>
<td>43</td>
<td>1.00</td>
<td>6.0</td>
<td>82</td>
<td>1.00</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>&lt;25</td>
<td>167</td>
<td>3.0</td>
<td>5</td>
<td>0.96 (0.4, 2.4)</td>
<td>3.6</td>
<td>6</td>
<td>1.07 (0.5, 2.5)</td>
<td>6.6</td>
<td>11</td>
</tr>
<tr>
<td>≥25</td>
<td>1286</td>
<td>3.1</td>
<td>40</td>
<td>1.00</td>
<td>3.3</td>
<td>43</td>
<td>1.00</td>
<td>6.5</td>
<td>83</td>
<td>1.00</td>
</tr>
<tr>
<td>SGA</td>
<td>105</td>
<td>2.9</td>
<td>5</td>
<td>0.98 (0.3, 3.1)</td>
<td>3.8</td>
<td>3</td>
<td>1.21 (0.4, 3.3)</td>
<td>6.7</td>
<td>7</td>
<td>1.10 (0.5, 2.3)</td>
</tr>
<tr>
<td>AGA</td>
<td>1298</td>
<td>2.9</td>
<td>38</td>
<td>1.00</td>
<td>3.2</td>
<td>41</td>
<td>1.00</td>
<td>6.1</td>
<td>79</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SGA indicates small for gestational age; AGA, appropriate for gestational age.

In both the gestational hypertension and preeclampsia groups, the median prepregnancy BMI was higher than in the reference group (23.2 [20.9, 28.4] and 23.1 [20.6, 25.9] versus 21.6 [19.6, 23.1] kg/m²; P<0.001). In the whole hypertensive group, 23% of women were overweight (BMI 25 to 30 kg/m²) and 15% obese (BMI ≥30 kg/m²) before their first pregnancy compared with 8% and 3% in the reference group (P=0.003).

Measures at Birth and Later Risk for Gestational Hypertension and Preeclampsia

Women born before the gestational week 37 had a 2-fold risk for gestational hypertension during first pregnancy (RR: 2.53; 95% CI: 1.0, 6.2) but no increased risk for preeclampsia (Table 1).

Participant Characteristics

Women in hypertensive groups more frequently had induced labor, cesarean section, preterm delivery (in preeclampsia), and lower-birth-weight infants (in preeclampsia) compared with the reference group. Mothers of women with preeclampsia had lower average parity in 1966 compared with mothers of reference group. Further details of the study population can be found in the online data supplement available at http://www.hypertensionaha.org.

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Results

Outcome characteristics were expressed as median with interquartile range (Q1, Q3). The nonparametric Mann-Whitney U test and regression analyses with and without adjustments for own birth weight and gestational age were used to compare outcomes between the gestational hypertension/preeclampsia and reference groups. Interactions of birth weight multiplied by gestational hypertension/ preeclampsia and gestational age multiplied by gestational hypertension/preeclampsia were examined in the regression models. The Kruskal-Wallis test was used for comparisons between 3 or more groups. Frequency distributions were assessed by cross-tabulations and Pearson χ² test for independence. Spearman correlation coefficient (ρ) was used to analyze correlation between variables.

Participant Characteristics

Women in hypertensive groups more frequently had induced labor, cesarean section, preterm delivery (in preeclampsia), and lower-birth-weight infants (in preeclampsia) compared with the reference group. Mothers of women with preeclampsia had lower average parity in 1966 compared with mothers of reference group. Further details of the study population can be found in the online data supplement available at http://www.hypertensionaha.org.

Participant background characteristics during first pregnancy and at age 31 years were not associated with either gestational hypertension or preeclampsia, although several were associated with metabolic outcome measures (data not shown). Consequently, these were not considered as confounders or intermediate factors in the final analyses. The median interval from first delivery to examination at 31 years was 6 years in all groups (range 5 months to 11 years). In the whole hypertensive group, the median first (<20 gestational weeks) systolic blood pressure and diastolic blood pressure of the index pregnancy was 120 (interquartile range 115, 128) and 72 mm Hg (interquartile range 68, 80) and the last before delivery were 145 (interquartile range 140,154) and 100 mm Hg (interquartile range 90, 102), respectively. The median maximum daily proteinuria throughout the pregnancy of women with preeclampsia was 1545 mg (interquartile range 726, 4537).

Blood Pressure, Anthropometric, Metabolic, and Biochemical Characteristics at Age 31

Compared with the reference group, the women with previous gestational hypertension had significantly (P<0.001 to P<0.04) higher BP, BMI, waist circumference, waist/hip ratio, insulin levels, and lower glucose/insulin ratio at age 31 years, although there were no significant differences in serum LDL, HDL, total cholesterol, or triglycerides (Table 2).

Women with preeclampsia also had significantly (P<0.01 to P<0.05) higher BP, insulin levels, and lower glucose/insulin ratio than the reference group (Table 2). Compared with the reference group, women with mild preeclampsia had higher BMI, waist circumference, and waist/hip ratio. Although BMI and other anthropometric measures of women with severe preeclampsia were similar to the reference group, blood glucose was higher (Table 2).
SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BMI, body mass index; Q₁, Q₃, interquartile range.

*Compared to reference group, Mann-Whitney U test.

Systolic BP (P<0.07), diastolic BP (P=0.16), and MAP (P<0.09) appeared to be higher in women with gestational hypertension compared with preeclampsia group, but no differences between these groups were found in other outcome measures.

Outcomes at age 31 were also assessed in the whole hypertensive group (Table 3). In this combined group, BP, BMI, waist circumference, waist/hip ratio, and insulin levels were higher and glucose/insulin ratio was lower, whereas serum triglycerides appeared to be higher (0.91 and 0.84 mmol/L, P=0.07) than in the reference group. Of the hypertensive group, 25% were overweight and 24% were obese compared with 23% and 8% of the reference group, respectively (P<0.001).

Adjustments for own birth weight did not change or modify the association between hypertensive pregnancies and the outcomes (reported in percentiles, Table 3), and the relevant interaction terms were statistically insignificant. Similarly, own gestational age did not modify this association.

There were positive significant (P<0.001) associations between BMI and MAP (p=0.26), serum insulin (ρ=0.42),

TABLE 3. Outcome Characteristics of the Women With Previous Hospital-Treated Gestational Hypertension (GH, n=45)/Preeclampsia (PE, n=49) and the Reference Group (Ref.) at the Age of 31 Years (Total N=1463)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Women N=1369</th>
<th>Women With Previous GH/PE N=94</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>117 (111, 125)</td>
<td>125 (117, 137)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74 (67, 80)</td>
<td>80 (71, 89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>88 (83, 94)</td>
<td>96 (87, 103)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.1 (21.1, 25.7)</td>
<td>24.5 (22.1, 29.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>77 (71, 84)</td>
<td>82 (72, 92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.80 (0.76, 0.84)</td>
<td>0.82 (0.77, 0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.70 (2.30, 3.20)</td>
<td>2.80 (2.40, 3.40)</td>
<td>0.148</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.61 (1.38, 1.84)</td>
<td>1.55 (1.36, 1.78)</td>
<td>0.344</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.72 (4.21, 5.35)</td>
<td>4.80 (4.32, 5.57)</td>
<td>0.310</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.84 (0.65, 1.18)</td>
<td>0.91 (0.73, 1.20)</td>
<td>0.067</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.90 (4.60, 5.10)</td>
<td>4.90 (4.70, 5.20)</td>
<td>0.046</td>
</tr>
<tr>
<td>Glucose/insulin ratio</td>
<td>0.67 (0.55, 0.81)</td>
<td>0.60 (0.50, 0.74)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Q₁, Q₃ indicates interquartile range; BW, women’s own birth weight in 1966; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

*Mann-Whitney U test, compared to reference women.

†Difference in outcome measures between GH/PE and reference group (antilog-transformed regression coefficient reported in percentages).
LDL cholesterol ($\rho=0.24$), triglycerides ($\rho=0.34$), glucose ($\rho=0.20$), and insulin/glucose ratio ($\rho=0.36$), and an inverse correlation between BMI and serum HDL cholesterol ($\rho=-0.29, P<0.001$) at age 31. After adjustment for BMI, the MAP ($P<0.001$), SBP ($P<0.001$), and DBP ($P<0.001$) were still higher in women with previous gestational hypertension compared with the reference group, as well as in women with preeclampsia ($P=0.023, P=0.023$, and $P=0.010$, respectively), whereas differences in other outcomes were nonsignificant (Table 3).

The results of a separate analysis of BP at age 31 of all females in the NFBC compared with the study groups are presented in Figure 2. BP of women with gestational hypertension ($P<0.001$) and preeclampsia ($P<0.05$) was higher compared with the whole female population, although after adjustment for socioeconomic position, basic education, and smoking at age 31 years, the difference was not statistically significant in the preeclampsia group ($P<0.07$). The women with previous normotensive pregnancy had lower BP compared with the whole female population ($P<0.001$, Figure 2).

### Discussion

This large, prospective population-based study of the relationships between early phenotypes, adult de novo hypertension during pregnancy, and insulin resistance with other features of the metabolic syndrome showed that women born preterm or of low birth weight were at slightly increased risk as adults for de novo hypertension during pregnancy; in turn, both gestational hypertension and preeclampsia are associated with an increased risk for features of metabolic disorder in later life. In women of childbearing age, high BP in pregnancy with or without proteinuria may be an early indicator of future risk of chronic disease.

The main strength of this study is the longitudinal and population-based nature of the data, from early life to young adulthood. Previous studies have not been able to link data collected at those different stages in life. We were able to analyze women with gestational hypertension and preeclampsia separately, and we were able to exclude women with chronic hypertension and to estimate the magnitude of misclassification of these cases in routine medical practice.

The hypertensive study group consisted of women with hospital-treated gestational hypertension and preeclampsia. We could not review obstetric records of all women; thus, women who had had gestational hypertension or chronic hypertension without hospitalization were included in the reference group. Based on our random sample, there were no preeclampsia cases observed in the reference group, although a few had milder gestational hypertension, which may slightly dilute the observed associations between the gestational hypertension/preeclampsia and reference group. The rate of gestational hypertension in our study represents only women with hospital-treated gestational hypertension but not all those with slightly elevated blood pressure during pregnancy. Because MBR data were available only from 1987 onwards, we had no information on $\sim 300$ first pregnancies occurring before age 20 years. We have thus probably missed some women with hypertensive pregnancy.

In our study, low birth weight and preterm birth were associated with a 2-fold risk of de novo hypertension during a woman’s first pregnancy, findings in parallel with the results of earlier studies by Innes et al (1999), who had,
It is widely accepted now that also preeclampsia and hypertension have an increased risk of hypertension later in life. It is known that women with previous gestational hypertension had higher BP at age 31 years compared with the whole female population of the Northern Finland 1966 Birth Cohort.

Both women with previous gestational hypertension and preeclampsia had higher BP at age 31 years compared with women with normotensive pregnancy, even after adjustment for BMI. It is known that women with previous gestational hypertension have an increased risk of hypertension later in life. It is widely accepted now that also preeclampsia predicts future chronic hypertension.

When compared with the whole female cohort, women with previous gestational hypertension had significantly higher BP at age 31, even after adjustment for socioeconomic position, basic education, and smoking. Findings in parallel with an earlier study by Adams et al (1961) and Chesley et al (1980) and Fisher et al (1981) have criticized the choice of only normotensive gravidas as “controls,” creating a population with an abnormally low remote incidence of high BP.

Our finding that women with normotensive pregnancy had lower BP than the female population at large confirm these earlier reports. However, in our study, women with previous preeclampsia had higher BP compared with the whole female population of same age, whereas Fisher et al (1981) found a similar prevalence of hypertension in 53 preeclamptic women examined 68 months after delivery, compared with that for age-, sex-, and race- adjusted statistics in a National Health Survey of the population at large.

Four studies suggest that women with preeclampsia have an increased risk for subsequent heart disease. Wilson et al (2003) found greater long-term cardiovascular risks for women who had preeclampsia than those who experienced gestational hypertension. A large registry study by Irgens et al (2001) found that women with preeclampsia have an increased risk for death from cardiovascular disease, with risk higher after preterm than term preeclamptic delivery. Note-worthy is that preterm preeclampsia also produces a population of low-birth-weight infants. However, all except two of these earlier studies were retrospective.

While some investigators view gestational hypertension and preeclampsia as differing severities of the same disorder, others consider these complications to be distinct syndromes with different cause. In our study, BP appeared to be higher in women with previous gestational hypertension compared with women with preeclampsia, but no other differences in metabolic syndrome features were found between these groups. However, glucose/insulin ratio, used as a marker of insulin resistance, was lower, and BMI, waist circumference, and waist/hip ratio were higher among women with previous gestational hypertension and preeclampsia compared with women with normotensive pregnancy. Although the BMI of women with previous severe preeclampsia was similar to that of the reference group at 31, they still had substantially higher BP and blood glucose compared with reference women.

Adjusting for own birth weight and gestational age did not materially change these results, nor was there an interaction between birth weight or gestational age and hypertension or preeclampsia. Overall associations were statistically marginal because of low power, especially when hypertensive groups were analyzed separately. Increased hypertensive pregnancy risk may partly be explained by genetic factors, ie, grandmother’s hypertensive pregnancy resulting in low birth weight and/or preterm delivery in 1966.

The differences in serum insulin and lipids between the groups disappeared after BMI adjustment. BMI adjustment in the analysis of metabolic syndrome is questionable because obesity is itself one expression of metabolic syndrome and has been shown to be associated with increased risk of preeclampsia. In our study, women with gestational hypertension and preeclampsia had higher BMI by the time of first pregnancy compared with the reference women, so may already have had a metabolic disorder. This could be related to the development of de novo hypertension during pregnancy. Obesity is the most powerful risk factor for type 2 diabetes. We studied metabolic syndrome features in young
adults, although the clinical manifestations of metabolic syndrome would usually manifest later; thus, ongoing surveillance of these women will be important as they reach middle age.

**Perspectives**

Women with preeclampsia and especially with gestational hypertension should be advised to have their BP measured and, as necessary, controlled after pregnancy. They should be informed about the increased risk for hypertension in subsequent pregnancies and later in life. The present study indicates that women with hypertensive pregnancy should also receive lifestyle counseling aimed at optimizing body weight and to control lipid and glucose levels in the postpartum period. Increased awareness of the association between insulin resistance and previous gestational hypertension/preeclampsia is needed among health care professionals to recognize, and forestall, possible risks among these women for future insulin-resistance syndrome, adult-onset diabetes, and cardiovascular diseases.

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**References**

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