Hypertension in Pregnancy and Later Cardiovascular Risk
Common Antecedents?

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Background—Preeclampsia and gestational hypertension are associated with increased risk for cardiovascular disease later in life. We have assessed whether the effect can be attributed to factors that operate in pregnancy or to prepregnancy risk factors that are shared by both disorders. Methods and Results—Longitudinal data from 2 consecutive waves of a Norwegian population-based study (the Nord-Trøndelag Health Study [HUNT]) were combined with data from the Medical Birth Registry of Norway. Among 24 865 women who had participated in both HUNT 1 and 2, we indentified 3225 women with a singleton birth between the 2 studies who had standardized measurements of blood pressure, serum lipids, and body mass index. The crude results showed that women who experienced preeclampsia or gestational hypertension in pregnancy had substantially higher levels of body mass index and systolic and diastolic blood pressures and unfavorable lipids compared with other women. However, after adjustment for prepregnancy measurements, the difference in body mass index was attenuated by >65%, and the difference in blood pressure was attenuated by ≈50%. In relation to high-density lipoprotein cholesterol and triglycerides, differences between the groups were attenuated by 40% and 72%, respectively. Conclusions—These results suggest that the positive association of preeclampsia and gestational hypertension with postpregnancy cardiovascular risk factors may be due largely to shared prepregnancy risk factors rather than reflecting a direct influence of the hypertensive disorder in pregnancy. (Circulation. 2010;122:579-584.)

Key Words: follow-up studies ▪ hypertension ▪ lipids ▪ preeclampsia ▪ risk factors

W
omen with a history of pregnancy-induced hypertension (including preeclampsia) are at increased risk of cardiovascular and metabolic diseases later in life.1–6 However, it is not known whether the increased risk can be attributed to factors that originate in pregnancy or to prepregnancy factors that are associated with both the risk of preeclampsia and gestational hypertension and the subsequent risk of cardiovascular and metabolic diseases.

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Several studies have reported that cardiovascular risk factors measured before pregnancy predict preeclampsia, suggesting that preeclampsia and cardiovascular disease may share common risk factors.7–9 Nonetheless, there is evidence that pregnancy factors may be causally related to cardiovascular risk; e.g., certain pregnancy conditions have been associated with cardiovascular and related diseases later in life.10

By studying risk factors for cardiovascular disease measured before and after pregnancy, we can separate pregnancy-related associations from associations that may be attributed to factors that are present before pregnancy. If the association of hypertension in pregnancy with subsequent cardiovascular risk factors is substantially attenuated after adjustment for prepregnancy risk factors, this could suggest that the association related to the hypertensive pregnancy is due mainly to a risk profile that is present before the pregnancy. However, the absence of attenuation or only weak attenuation may suggest that pregnancy-induced hypertension could increase the risk of later cardiovascular disease.

To distinguish between shared factors and factors that are unique to pregnancy, we used data from a population study of parous women for whom body mass index (BMI) and blood pressure were measured both before and after pregnancy.

Methods

The present study is based on a linkage between women who participated in 2 waves of the Nord-Trøndelag Health Study (HUNT) in Norway (HUNT 1 and HUNT 2)11 and the Medical Birth Registry of Norway.12 HUNT 1 and 2 include residents ≥20 years of age in Nord-Trøndelag County. The first wave (HUNT 1, 1984 to 1986) included 74 899 subjects and had a participation rate of ≈88%, and the second wave (HUNT 2, 1995 to 1997) included 65 604 individuals who constituted 71% of the total adult population.

Both surveys included standardized measurements of height, weight, and blood pressure. Information on lifestyle factors such as smoking history, socioeconomic position, and educational attain-
ment was collected by self-administered questionnaires. HUNT 2 also included measurements of nonfasting serum lipids. Since 1967, all deliveries in Norway (>2 million births) have been recorded in the Medical Birth Registry of Norway. The registration is based on standardized forms completed by midwives at the delivery ward within 1 week after delivery. The reporting is mandatory and covers virtually all deliveries in Norway. The form gives information related to the mother’s health before and during pregnancy and complications during pregnancy and at birth.

In total, 24,865 women participated in both waves of the HUNT Study. By linking these women to the Medical Birth Registry using the unique person number of every Norwegian citizen, we found that 14,131 women were registered with a birth between 1967 and 2005. Among these women, 3,356 had given birth during the interval between HUNT 1 and HUNT 2, and among them, 261 women had experienced hypertension in pregnancy. Among the 3,356 women with a registered birth between surveys, we excluded 86 who were pregnant at the data collection of HUNT 2 and 42 women with missing information on essential measurements. Thus, a total of 3,225 women were included in the analysis of the present study.

In Norway, antenatal care is free of cost and well standardized, and nearly 100% of all pregnant women attend antenatal care, which usually includes ~12 visits to a midwife or to a general practitioner during pregnancy. At each visit, blood pressure is measured and urine is analyzed for protein with a semiquantitative dipstick.

The diagnostic criteria for preeclampsia follow the 1972 recommendations of the American College of Obstetricians and Gynecologists. Thus, preeclampsia is defined as a sustained increase in blood pressure to at least 140/90 mm Hg after midgestation, combined with proteinuria of at least 1+ or more on a semiquantitative dipstick, and hypertension and proteinuria should be apparent on 2 different occasions at least 4 to 6 hours apart. The diagnostic criteria have remained fairly constant since 1967. Clinical criteria for gestational hypertension are also in accordance with the 1972 recommendations of the American College of Obstetricians and Gynecologists. Thus, gestational hypertension is defined as blood pressure ≥140/90 mm Hg or an increase in systolic blood pressure ≥30 mm Hg and diastolic blood pressure ≥15 mm Hg after midgestation in at least 2 readings ≥6 hours apart without concomitant proteinuria.

**HUNT Measurements**

Height and weight were measured by specially trained nurses with the participants wearing light clothes (no outer garments) and without shoes. Height was recorded to the nearest centimeter and weight to the nearest half kilogram. BMI was calculated as weight divided by the squared value of height.

In HUNT 1, diastolic and systolic blood pressures were measured twice with a sphygmomanometer; in HUNT 2, standardized blood pressure was measured 3 times at 1-minute intervals with an automatic oscillometric method (Dinamap 845XT; Criticon, Tampa, Fla). At both surveys, blood pressure was measured after a minimum of 2 minutes’ rest in the sitting position. We used the mean of the 2 readings from HUNT 1 and the mean of the second and third readings from HUNT 2 in the analyses.

HUNT 2 also included a nonfasting blood sample, and total serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were subsequently analyzed. Time since last meal was recorded before blood sampling. HDL cholesterol was measured after precipitation with phosphor tungsten and magnesium ions. Triglycerides were measured with an enzymatic colorimetric method. The day-to-day coefficients of variation were 1.3% to 1.9% for total cholesterol, 2.4% for HDL cholesterol, and 0.7% to 1.3% for triglycerides.

**Statistical Analyses**

We estimated adjusted mean blood pressure and mean lipid concentrations according to preeclampsia and gestational hypertension using multiple linear regression analysis with 95% confidence intervals (CIs). We divided the women into 3 categories: women with a history of gestational hypertension, women with a history of preeclampsia, and women with normotensive pregnancies. The 3 group comparisons were adjusted for multiple comparisons with the Bonferroni correction. All analyses were adjusted for age at HUNT 2 in 5-year categories; in separate analyses, we also adjusted for time interval (years) and number of children born between the surveys (HUNT 1 and HUNT 2), smoking status (never, former, current) at HUNT 2, level of education (<9, 9 to 12, 12 to 14, and >14 years) at HUNT 2, and requirement of social security benefits (yes/no) at HUNT 2. In the analyses of serum lipids, we also included time since last meal as a covariate. In additional analyses, adjustments were made for prepregnancy measurements at HUNT 1 of BMI and systolic and diastolic blood pressures.

Stata version 10.0 for Windows (Stata Corp, College Station, Tex) was used for the statistical analyses. The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate. All study participants signed a form giving their informed consent for study participation.

**Results**

Women with a history of preeclampsia or gestational hypertension and women without this experience were of similar age and educational background (Table 1). However, they were more often nonsmokers, had fewer previous births, had higher blood pressure, and tended more often to be users of blood pressure medication; these differences were independent of whether the information was collected before or after pregnancy.

Mean age-adjusted BMI at follow-up in HUNT 2 was higher in the pregnancy hypertension groups (Table 2), and these differences persisted after additional adjustment for other factors measured at HUNT 2. However, after adjustment for prepregnancy BMI, the difference in BMI after pregnancy was attenuated by >65% (Table 3).

Differences in systolic and diastolic blood pressures at follow-up in HUNT 2 showed patterns similar to BMI (Table 4). Whereas the age-adjusted difference in systolic blood pressure was greater in women with a history of preeclampsia or gestational hypertension (12 mm Hg; 95% CI, 10 to 13 mm Hg), the difference was reduced by nearly 50% after adjustment for prepregnancy blood pressure (6 mm Hg; 95% CI, 5 to 8 mm Hg). Excluding women who reported ever using blood pressure medication before participation in HUNT 1 (n=56), who reported chronic hypertension at HUNT 1 (n=44), or who reported diabetes at follow-up in HUNT 2 did not substantially change these results.

We also found that women with hypertension in pregnancy more often had unfavorable serum lipid levels in HUNT 2 (Table 5). However, after adjustment for prepregnancy BMI, the difference in serum triglycerides was nearly fully attenuated, and for HDL cholesterol, the difference was reduced from −0.10 to −0.06 mmol/L after adjustment for prepregnancy factors.

To reflect BMI trajectories that had started before the pregnancy, we also performed analyses adjusted for BMI at the time of blood pressure and lipid measurement. The analysis showed additional attenuation in the association of preeclampsia or gestational hypertension with unfavorable lipid levels and blood pressure (Table 5). Thus, the difference in HDL cholesterol between the groups was further attenuated (~0.04 mmol/L; 95% CI, −0.08 to 0.002) after these additional adjustments. We also studied whether hypertension in >1 pregnancy could influence the
results. Although there was a tendency for repeated episodes of pregnancy hypertension to be associated with larger differences in cardiovascular risk factors between the groups, there was a similar degree of attenuation after adjustment for prepregnancy factors. Because few women (n=25) had experienced repeated hypertensive disorders in pregnancy, these results should be interpreted with caution (results not tabulated).

<table>
<thead>
<tr>
<th>Table 1. Prepregnancy (HUNT 1) and Postpregnancy (HUNT 2) Characteristics of 3225 Women According to Hypertensive Disorders* in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Hypertensive Disorder* (n=2964)</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
</tr>
</tbody>
</table>
| Smoking,‡ n (%)
  Never | 1032 (41) | 123 (56) | 1228 (41) | 139 (53) |
  Former | 496 (20) | 31 (14) | 726 (25) | 58 (22) |
  Current | 986 (39) | 66 (30) | 1010 (34) | 64 (25) |
| Education,‡ n (%)
  <12 y | 1572 (63) | 139 (63) | 1721 (58) | 155 (59) |
  12–13 y | 497 (20) | 42 (19) | 438 (15) | 30 (12) |
  ≥14 y | 428 (17) | 39 (18) | 805 (27) | 76 (29) |
| Previous births, n (%)
  0 | 786 (26) | 108 (41) | 0 (0) | 0 (0) |
  1 | 1090 (37) | 76 (29) | 190 (6) | 22 (8) |
  ≥2 | 1088 (37) | 77 (30) | 2774 (94) | 239 (92) |
| Blood pressure medication, n (%)
  Current/former | 36 (1) | 20 (8) | 69 (2) | 60 (23) |
  Never | 2928 (99) | 241 (92) | 2895 (98) | 201 (77) |
| Diabetes mellitus, n (%)
  No | 2962 (99.1) | 260 (99.6) | 2945 (99.4) | 256 (99.3) |
  Yes | 2 (0.1) | 1 (0.4) | 19 (0.6) | 5 (1.9) |
| Mean (SD) BMI, kg/m² | 22.5 (3.0) | 24.1 (3.7) | 25.0 (3.9) | 27.4 (1.9) |
| Mean (SD) systolic BP, mm Hg | 117 (11) | 126 (13) | 122 (13) | 133 (17) |
| Mean (SD) diastolic BP, mm Hg | 74 (9) | 81 (9) | 74 (9) | 81 (11) |

BP indicates blood pressure.

*Preeclampsia or gestational hypertension.

†In HUNT 1, 491 women had missing information on smoking status.

‡In HUNT 1, 508 women had missing data on education.

Table 2. Adjusted Mean BMI and Waist Circumference at Follow-Up (HUNT 2, 1995 to 1997) According to Preeclampsia or Gestational Hypertension and Adjustment for Prepregnancy BMI in HUNT 1 (1984 to 1986)

<table>
<thead>
<tr>
<th>Preeclampsia or Gestational Hypertension Between the HUNT 1 and HUNT 2 Surveys</th>
<th><strong>BMI in HUNT 2, kg/m²</strong></th>
<th><strong>Waist, cm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted*</td>
<td>Follow-Up Adjusted†</td>
</tr>
<tr>
<td>Normotensive</td>
<td>3057</td>
<td>25.3</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>93</td>
<td>27.8</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>168</td>
<td>27.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prepregnancy or gestational hypertension</th>
<th><strong>BMI in HUNT 2, kg/m²</strong></th>
<th><strong>Waist, cm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2964</td>
<td>25.3</td>
</tr>
<tr>
<td>Yes</td>
<td>261</td>
<td>27.7</td>
</tr>
</tbody>
</table>

*Adjusted for age at follow-up.

†Adjusted for age at follow-up, parity at first birth after HUNT 1, education, smoking, receiving social security benefits, and time since last meal in HUNT 2. All P values for differences in mean according to preeclampsia or gestational hypertension were <0.001 in the crude and the follow-up adjusted analyses.

‡Additional adjustment for prepregnancy BMI (measured in HUNT 1).

§All P values were corrected for multiple comparisons with the Bonferroni correction.
Between the HUNT 1 and HUNT 2 Surveys

Table 4. Adjusted Mean Level of Systolic and Diastolic Blood Pressures at Follow-Up in HUNT 2 (1995 to 1997) According to Preeclampsia or Gestational Hypertension and Adjustment for Prepregnancy Blood Pressure in HUNT 1 (1984 to 1986)

<table>
<thead>
<tr>
<th>Variable Measured in HUNT 2</th>
<th>Prepregnancy-Adjusted Difference†</th>
<th>Additional Adjustment for BMI Measured in HUNT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-Up Adjusted Difference†</td>
<td>Age-Adjusted Difference*</td>
</tr>
<tr>
<td></td>
<td>Difference 95% CI Attenuation, %</td>
<td>Difference 95% CI Attenuation, %</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Mean†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>11.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>-0.09</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

*Age adjusted.
†Adjusted for age at follow-up, parity at first birth after HUNT 1, education, smoking, receiving social security benefits in HUNT 2, and time (hours) since last meal for triglycerides and HDL cholesterol.
‡Additional adjustment for prepregnancy BMI and systolic and diastolic blood pressures measured in HUNT 1.

Discussion

In this prospective population study, the association of preeclampsia or gestational hypertension with BMI and blood lipids measured after pregnancy was substantially attenuated after adjustment for prepregnancy cardiovascular risk factors. A similar attenuation was found for systolic and diastolic blood pressures. Because of measurement error in the prepregnancy risk factors, these attenuations are likely to be underestimates of the true attenuations. Our results suggest that the association of hypertension in pregnancy with later cardiovascular risk factor levels may be largely attributed to risk factors that were present before pregnancy, not to the pregnancy condition itself.

Our study has several strengths. The large numbers and standardized clinical measurements secure high precision of the findings, and the comprehensive questionnaire data from the HUNT studies allow control of many relevant potentially confounding factors such as smoking habits and socioeconomic factors, including education. The longitudinal study design makes recall and selection bias unlikely, and the population-based sampling, including high attendance, suggests that the findings may be generalized to other populations.

The women had to participate in the 2 first waves of HUNT (HUNT 1 and HUNT 2) to be included in the analyses. This could have introduced a potential bias as a result of selective survival. However, only a small proportion (0.6%) of women at fertile age died between the surveys, and a separate analysis showed no substantial differences between women who attended and women who did not attend HUNT 2 with respect to mean levels of BMI and blood pressure measured at HUNT 1.

The nonfasting blood sampling is another potential limitation of the study. We attempted to correct for this weakness by adjusting for time since last meal, but the results were not substantially altered. Nonetheless, we cannot exclude the possibility of nondifferential bias related to the nonfasting sampling of blood lipids. As in all observational studies, the
possible role of uncontrolled or residual confounding should also be considered.

Many large cohort studies have linked a history of hypertensive disorder in pregnancy with future risk of cardiovascular and cerebrovascular diseases, suggesting that both conditions may have common underlying causes. The results of other studies suggest that cardiovascular risk factors measured before pregnancy may predict preeclampsia but we are not aware of any other studies that have considered the role of factors measured both before and after pregnancy.

It is possible that inaccurate diagnosis of preeclampsia and gestational hypertension could represent nondifferential bias in this study; eg, there may be some underreporting of gestational hypertension, and mild preeclampsia could be misclassified as gestational hypertension (and vice versa) in the Medical Birth Registry. To address the latter possibility, we conducted separate analyses for preeclampsia and gestational hypertension, and we combined the 2 conditions into 1 category (preeclampsia or gestational hypertension). There are no formal validation studies of the diagnoses of preeclampsia or gestational hypertension in the Medical Birth Registry of Norway. However, a validation of the similar Swedish Birth Registry data suggested that these diagnoses were of high validity, with positive predictive values for gestational hypertension and preeclampsia of 93% and 84%, respectively.

If the prepregnancy risk factors were measured with higher precision, the associations that we report could have been attenuated even further. For example, the instruments that measured blood pressure were different in HUNT 1 and HUNT 2. In the analyses, we used the mean of the 2 blood pressure readings from HUNT 1 and the mean of the second and third readings from HUNT 2. Still, the association of a hypertensive pregnancy with later cardiovascular risk factors was attenuated by >50% after adjustment for factors measured before pregnancy, including BMI and blood pressure.

The degree of attenuation after adjustment appeared to be greater for BMI than for blood pressure. Whether this reflects that BMI could have a stronger attenuating effect or that BMI may be measured more precisely is not clear.

The potential mechanisms that may link hypertensive disorders in pregnancy with future cardiovascular disease are not well understood. Many large cohort studies have suggested that these conditions could share common underlying causes such as obesity, dyslipidemia, insulin resistance, and endothelial dysfunction. However, it is also possible that the hypertensive pregnancy disorder itself could induce irreversible vascular and metabolic changes that are associated with increased risk of CVD. A pregnancy involves a range of physiological and metabolic changes, including a certain degree of insulin resistance, lipid alterations, and upregulation of inflammatory markers that may be exaggerated in hypertensive pregnancies. Thus, systemic endothelial dysfunction is an important characteristic of preeclampsia, maybe causing long-term effects.

We attempted to distinguish between mechanisms that are unique to pregnancy and risk factors that were present before pregnancy. Our results suggest that the contribution to cardiovascular risk of a hypertensive pregnancy is smaller than the contribution of factors that were present before pregnancy. Nonetheless, our results cannot exclude the possibility that preeclampsia and gestational hypertension are associated with later risk of cardiovascular disease, regardless of prepregnancy risk factors.

### Conclusions

The results of this study suggest that cardiovascular risk factors that are present before a hypertensive pregnancy are more important determinants of subsequent cardiovascular risk factors than the hypertensive pregnancy itself. Therefore, our results suggest that the maternal constitution is a key factor in relation to both the risk of developing preeclampsia or gestational hypertension and the later risk of cardiovascular disease.

### Acknowledgments

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Disclosures
None.

References


CLINICAL PERSPECTIVE
Gestational hypertension and preeclampsia are common disorders in pregnancy, and both disorders have been associated with a substantially increased risk of cardiovascular disease later in life. Therefore, hypertension in pregnancy may provide a unique opportunity for the clinicians to identify women at an early stage who may be at increased risk of future cardiovascular disease. It is uncertain, however, whether the association of hypertensive pregnancy disorders with cardiovascular disease can be attributed to factors that operate in pregnancy or to prepregnancy factors that are associated with both the pregnancy condition and later cardiovascular disease. We linked data from the Medical Birth Registry of Norway to 2 waves of a large population-based health survey in Norway (the Nord-Trøndelag Health Study [HUNT]) and prospectively examined the association of hypertensive disorders in >3225 pregnancies with subsequent measurements of body mass index, blood pressure, and serum levels of high-density lipoprotein cholesterol and triglycerides; we simultaneously adjusted for prepregnancy measurements of the same factors. We found that the associations of hypertensive disorders in pregnancy with subsequent body mass index and blood lipids were considerably attenuated after adjustment for risk factors measured before pregnancy. The results of this study suggest that the positive association of preeclampsia and gestational hypertension with later unfavorable cardiovascular risk factors may be due largely to shared prepregnancy risk factors such as obesity, dyslipidemia, and elevated blood pressure rather than reflecting factors that can be attributed to the hypertensive pregnancy.
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