Association Between Hypertensive Disorders of Pregnancy and Later Risk of Cardiomyopathy

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IMPORTANCE Women with hypertensive disorders of pregnancy, preeclampsia in particular, have an increased risk of cardiomyopathy during the peripartum period. Whether hypertensive disorders of pregnancy are also associated with cardiomyopathy later in life is unknown.

OBJECTIVE To determine whether hypertensive disorders of pregnancy are associated with cardiomyopathy beyond the peripartum period.

DESIGN, SETTING, AND PARTICIPANTS Nationwide register-based cohort study using Cox regression to compare rates of cardiomyopathy in women with and without a history of hypertensive disorders of pregnancy in a cohort of 1,075,763 women with at least 1 pregnancy ending in live birth or stillbirth in Denmark, 1978-2012, with follow-up through December 31, 2012.

EXPOSURES A hypertensive disorder of pregnancy (severe or moderate preeclampsia or gestational hypertension) registered in the National Patient Register.

MAIN OUTCOMES AND MEASURES Cardiomyopathy more than 5 months after delivery (outside the peripartum period) up to 34 years 7 months.

RESULT The women in the primary cohort had 2,067,633 eligible pregnancies during the study period, 76,108 of which were complicated by a hypertensive disorder of pregnancy. During follow-up, 1,577 women (mean age, 48.5 years at cardiomyopathy diagnosis; 2.6% with multiple pregnancies) developed cardiomyopathy. Compared with women with normotensive pregnancies (18,211,603 person-years of follow-up; n = 1408 cardiomyopathy events; 7.7/100,000 person-years [95% CI, 7.3-8.2]), women with a history of hypertensive disorders of pregnancy had significantly increased rates of cardiomyopathy (in 173,062 person-years of follow-up among women with severe preeclampsia, n = 27 cardiomyopathy events; 15.6/100,000 person-years [95% CI, 10.7-22.7]; adjusted hazard ratio [HR], 2.20 [95% CI, 1.50-3.23]; in 697,447 person-years of follow-up among women with moderate preeclampsia, n = 102 cardiomyopathy events; 14.6/100,000 person-years [95% CI, 12.0-17.8]; adjusted HR, 1.89 [95% CI, 1.55-2.23]; in 213,197 person-years of follow-up among women with gestational hypertension, n = 40 cardiomyopathy events; 17.3/100,000 person-years [95% CI, 12.7-23.6]; adjusted HR, 2.06 [95% CI, 1.50-2.82]). These increases persisted more than 5 years after the latest pregnancy. Mediation analyses suggested that only about 50% of the association was an indirect association through postpregnancy chronic hypertension. In this cohort, 11% of all cardiomyopathy events occurred in women with a history of hypertensive disorders of pregnancy.

CONCLUSIONS AND RELEVANCE Women with a history of hypertensive disorders of pregnancy, compared with women without such a history, had a small but statistically significant increased risk of cardiomyopathy more than 5 months after delivery. Further research is necessary to understand whether there is a causal mechanism behind this association.
Hypertensive disorders of pregnancy (HDP), which include preeclampsia and gestational hypertension, are characterized by de novo hypertension, with or without abnormal biochemical findings, in the second half of pregnancy and occur in up to 10% of pregnancies worldwide. 1,2 In severe cases, preeclampsia can lead to multiple organ failure, seizures (eclampsia), and fetal and maternal death. 3

Women with preeclampsia have a greatly increased risk of cardiomyopathy in the peripartum period (the last month of pregnancy until 5 months after delivery). 4-6 Peripartum cardiomyopathy is an idiopathic pregnancy-related cardiomyopathy often characterized by severely reduced myocardial contractility and symptoms of heart failure. 6 Preeclampsia is also associated with cardiovascular disease later in life; women with a history of preeclampsia have 3 to 4 times the risk of hypertension and twice the risk of ischemic heart disease and cerebrovascular disease years after the affected pregnancy, 7-11 risks that may increase with preeclampsia severity. 8-10 Whether women with a history of preeclampsia also have an increased risk of cardiomyopathy outside the peripartum period is unknown, but recent findings of persistent cardiac dysfunction and remodeling after preeclampsia suggest that such an association is plausible. 12,13 The etiology of preeclampsia and the link between preeclampsia and cardiovascular disease are poorly understood, but shared underlying mechanisms may be involved in the pathophysiology of preeclampsia and pregnancy-related cardiac/cardiovascular damage. 14,15

It was hypothesized that women with a history of HDP are at increased risk of cardiomyopathy not only in the peripartum period but also years after pregnancy and that the magnitude of the association increases with the severity of the HDP. A nationwide register-based cohort study was conducted to investigate the association between HDP and cardiomyopathy after the peripartum period.

Methods

Study Cohort

Using the National Patient Register and the Medical Birth Register (see eMethods in the Supplement), all women in Denmark with at least 1 pregnancy ending in live birth or stillbirth between 1978 and 2012 were identified (Figure). Pregnancies with gestational length less than 20 weeks and women registered with any cardiovascular disease (including hypertension) or diabetes mellitus more than 1 month before their first registered delivery were excluded (Figure; eMethods in the Supplement). The study was approved by the Danish Data Protection Agency; neither informed consent nor ethics committee approval are required for strictly register-based research.

Hypertensive Disorders of Pregnancy (Exposure)

A woman was considered to have an HDP in a given pregnancy if she was registered with gestational hypertension, moderate preeclampsia or severe preeclampsia (including eclampsia and HELLP syndrome [hemolysis, elevated liver enzymes, low platelet count]) in the National Patient Register any time between 1 month before delivery and 7 days postpartum. By definition, gestational hypertension and preeclampsia involve de novo hypertension in a pregnant woman, with onset after 20 weeks’ gestation. 1,16 As registered in the National Patient Register, gestational hypertension is defined as hypertension without accompanying proteinuria, whereas in moderate preeclampsia, mild to moderate hypertension is accompanied by proteinuria. Severe preeclampsia fulfills the criteria for moderate preeclampsia, with the addition of severe hypertension and/or severe proteinuria and/or signs of organ failure (which can include the HELLP syndrome) and/or generalized seizures (eclampsia) (see eMethods in the Supplement). To try to ensure that HDP diagnoses reflected true cases, women whose only HDP diagnoses were registered more than 1 month before or more than 7 days after delivery were not considered to have had an HDP.

HDP status was handled as a time-dependent variable. A woman could contribute person-time to several exposure groups, changing her exposure status if a given pregnancy was more complicated (in terms of HDP) than a previous pregnancy (but not if the pregnancy was less complicated—she could only become more severely affected) (eMethods and eFigure in the Supplement).

In sensitivity analyses, classification of preeclampsia based on gestational length at delivery was also investigated. Preeclampsia (any registered diagnosis code, regardless of severity) was classified as early preterm if delivery occurred at less than 34 completed weeks’ gestation and late preterm/term when delivery occurred at 34 or more completed weeks’ gestation.
Cardiomyopathy (Outcome)
A woman was considered to have cardiomyopathy after the peripartum period if she was registered in the National Patient Register or Causes of Death Register with cardiomyopathy (eMethods in the Supplement) more than 5 months after delivery, in the absence of peripartum cardiomyopathy, up to 34 years 7 months of follow-up. Subanalyses then focused specifically on dilated cardiomyopathy, the cardiomyopathy phenotype typically seen in the peripartum period. Furthermore, since some cases of cardiomyopathy could have been coded as heart failure, particularly before echocardiography became a widely used diagnostic tool (in the mid-1990s), parallel supplemental analyses for heart failure were conducted (eMethods in the Supplement).

Covariates
Two groups of covariates were considered: variables considered a priori to be potential confounders (birth year, age, smoking, parity, multiple pregnancy, stillbirth) and variables that might be confounders but might also be intermediate linking HDP and cardiomyopathy or competing causes of cardiomyopathy (postpregnancy diabetes, ischemic heart disease, hypertension, obesity) (eMethods in the Supplement). The latter are all associated with HDP,3,9,17 and associations with cardiomyopathy are also plausible. Women registered with cardiovascular disease or diabetes before their first pregnancy in the study period were excluded. Obesity and incident postpartum diabetes were judged to be true potential confounders. Although the reduced age as the underlying time scale was used to estimate hazard ratios (HRs) comparing rates of cardiomyopathy for women with a history of HDP and women with normoten-

Statistical Analyses
Women were followed up from 5 months after their first delivery in the study period to the first of the following events: (1) cardiomyopathy; (2) death; (3) emigration; (4) designated “missing” in the Civil Registration System; or (5) December 31, 2012 (the end of follow-up). Women with more than 1 pregnancy during the follow-up period contributed follow-up time during and after all pregnancies subsequent to the first, but the peripartum time associated with any subsequent pregnancies (1 month before delivery to 5 months after delivery) was excluded from the analyses. Women who developed peripartum cardiomyopathy (cardiomyopathy in the peripartum period) were censored and did not contribute further follow-up time.

Cox proportional hazards modeling with the woman’s age as the underlying time scale was used to estimate hazard ratios (HRs) comparing rates of cardiomyopathy for women with a history of HDP and women with normoten-

Results
The primary cohort consisted of 1,075,763 women with 2,067,633 pregnancies ending in live birth or stillbirth during the study period. Of these pregnancies, 12,974 were complicated by severe preeclampsia, 44,711 by moderate preeclampsia, and 18,423 by gestational hypertension. The cohort was followed up for 19.3 million person-years (mean, 17.9 years per woman). Of the 1577 women who developed cardiomyopathy during follow-up, 169 (10.7%) had a history of HDP. A total of 26,945 women (2.5%) were lost to follow-up; the majority of these women (26,399) moved abroad. Table 1 reports characteristics of each woman’s first pregnancy in the study period by HDP status; eTable 1 in the Supplement reports these characteristics for women lost to follow-up. During follow-up, 19 (0.20%)
women with severe preeclampsia, 84 (0.26%) with moderate preeclampsia, 29 (0.25%) with gestational hypertension, and 1445 (0.14%) with no HDP in their first pregnancy developed cardiomyopathy.

Comparing rates of cardiomyopathy for women with a history of HDP and rates for women with a history of only normotensive pregnancies yielded HRs of 2.20 (95% CI, 1.50-3.23) for severe preeclampsia, 1.89 (95% CI, 1.55-2.32) for moderate preeclampsia, and 2.06 (95% CI, 1.50-2.82) for gestational hypertension (Table 2). Even more than 5 years after a woman’s last pregnancy in the study period, HRs were 2.22 (95% CI, 1.47-3.36) for severe preeclampsia, 1.86 (95% CI, 1.50-2.30) for moderate preeclampsia, and 2.25 (95% CI, 1.63-3.09) for gestational hypertension (Table 2). When the analyses were stratified by current age younger than 45 years and 45 years or older, the HRs for the 2 age groups were not statistically significantly different (P = .09). (9.2 cardiomyopathy events/100 000 person-years [95% CI, 7.3-11.6] among women <45 years with a history of HDP and 3.6/100 000 person-years [95% CI, 3.3-4.0] among women <45 years with no history of HDP; HR, 2.35 [95% CI, 1.83-3.01]; 30.4 cardiomyopathy events/100 000 person-years [95% CI, 24.9-37.1] among women ≥45 years with a history of HDP and 17.8/100 000 person-years [95% CI, 16.7-19.0] among women ≥45 years with no history of HDP; HR, 1.77 [95% CI, 1.43-2.18]). Limiting the focus to dilated cardiomyopathy produced similar results (Table 3); wider confidence intervals reflect the reduced number of outcomes in this subcohort. When women with early preterm preeclampsia (16.3 cardiomyopathy events/100 000 person-years [95% CI, 8.2-32.6]) and late preterm/term preeclampsia (14.7 cardiomyopathy events/100 000 person-years [95% CI, 12.2-17.7]) were compared with women with no history of HDP (7.6 cardiomyopathy events/100 000 person-years [95% CI, 7.2-8.0]), the respective HRs were 2.29 (95% CI, 1.14-4.60) and 1.96 (95% CI, 1.61-2.38).

Adjusting for diabetes diagnosed during the follow-up period, and stopping follow-up if ischemic heart disease was diagnosed, did not change the magnitudes of the observed associations (Table 4). Further adjustment for smoking also did not affect the strength of the estimates (eTable 2 in the Supplement). Considering only HDP status in a woman’s first pregnancy resulting in live birth or stillbirth during 1991 and 2012.

### Table 1. Characteristics of a Woman’s First Pregnancy in the Study Period Resulting in Live Birth or Stillbirth, Denmark, 1978-2012 (Unless Otherwise Specified)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe Preeclampsia*</th>
<th>Moderate Preeclampsiaa</th>
<th>Gestational Hypertensionb</th>
<th>Normotensive Pregnancy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>402 (6.52)</td>
<td>1451 (4.62)</td>
<td>279 (2.51)</td>
<td>46 761 (4.57)</td>
<td>48 919 (4.55)</td>
</tr>
<tr>
<td>20-24</td>
<td>2253 (23.8)</td>
<td>8807 (28.1)</td>
<td>2455 (22.0)</td>
<td>273 622 (26.7)</td>
<td>287 137 (26.7)</td>
</tr>
<tr>
<td>25-29</td>
<td>3634 (38.4)</td>
<td>12 086 (38.5)</td>
<td>4295 (38.6)</td>
<td>411 602 (40.2)</td>
<td>431 617 (40.1)</td>
</tr>
<tr>
<td>30-34</td>
<td>2188 (23.1)</td>
<td>6260 (20.0)</td>
<td>2691 (24.2)</td>
<td>216 164 (21.1)</td>
<td>227 303 (21.1)</td>
</tr>
<tr>
<td>≥35</td>
<td>966 (10.2)</td>
<td>2782 (8.86)</td>
<td>1417 (12.7)</td>
<td>75 622 (7.39)</td>
<td>80 787 (7.51)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>638 (6.74)</td>
<td>1243 (3.96)</td>
<td>250 (2.24)</td>
<td>16 376 (1.60)</td>
<td>18 507 (1.72)</td>
</tr>
<tr>
<td>No</td>
<td>8831 (93.3)</td>
<td>30 143 (96.0)</td>
<td>10 887 (97.8)</td>
<td>1 007 395 (98.4)</td>
<td>1 057 256 (98.3)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>138 (1.46)</td>
<td>144 (0.46)</td>
<td>58 (0.52)</td>
<td>4916 (0.48)</td>
<td>5258 (0.49)</td>
</tr>
<tr>
<td>No</td>
<td>9331 (98.5)</td>
<td>31 242 (99.5)</td>
<td>11 079 (99.5)</td>
<td>1 018 853 (99.5)</td>
<td>1 070 505 (99.5)</td>
</tr>
<tr>
<td>Smoking status (1991-2012)d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>892 (13.3)</td>
<td>3175 (17.6)</td>
<td>1076 (15.6)</td>
<td>165 361 (23.9)</td>
<td>170 504 (23.6)</td>
</tr>
<tr>
<td>No</td>
<td>5822 (86.7)</td>
<td>14 907 (82.4)</td>
<td>5831 (84.4)</td>
<td>526 443 (76.1)</td>
<td>553 003 (76.4)</td>
</tr>
<tr>
<td>Total</td>
<td>6714</td>
<td>18 082</td>
<td>6907</td>
<td>691 804</td>
<td>723 507</td>
</tr>
<tr>
<td>Prepregnancy BMI (2004-2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>115 (3.62)</td>
<td>151 (2.07)</td>
<td>70 (1.83)</td>
<td>14 232 (4.48)</td>
<td>14 568 (4.39)</td>
</tr>
<tr>
<td>18.5-24</td>
<td>1806 (56.9)</td>
<td>3577 (48.9)</td>
<td>1790 (46.7)</td>
<td>204 874 (64.5)</td>
<td>212 047 (63.9)</td>
</tr>
<tr>
<td>25-29</td>
<td>731 (23.0)</td>
<td>1935 (26.5)</td>
<td>1012 (26.4)</td>
<td>64 258 (20.2)</td>
<td>67 936 (20.5)</td>
</tr>
<tr>
<td>30-34</td>
<td>315 (9.92)</td>
<td>981 (13.4)</td>
<td>550 (14.4)</td>
<td>22 926 (7.2)</td>
<td>24 772 (7.47)</td>
</tr>
<tr>
<td>≥35</td>
<td>209 (6.58)</td>
<td>665 (9.10)</td>
<td>410 (10.7)</td>
<td>11 157 (3.51)</td>
<td>12 441 (3.75)</td>
</tr>
<tr>
<td>Total</td>
<td>3176</td>
<td>7309</td>
<td>3832</td>
<td>317 447</td>
<td>331 764</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

- ICD-8 codes 637.03, 637.09, or 637.99; ICD-10 codes O14.0 or O14.9.
- ICD-8 code 637.00; ICD-10 codes O13.0-13.9 or O16.0-16.9.
- Smoking status in the first trimester (yes: smoking during some or all of the first trimester) in a woman’s first pregnancy resulting in live birth or stillbirth between 1991 and 2012.
Table 2. Hazard Ratios for Dilated Cardiomyopathy More Than 5 Months After First Delivery by History of Hypertensive Disorders of Pregnancy, Denmark, 1994-2012a,b

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No. of Women</th>
<th>Person-Years ×10^6</th>
<th>Events, No.</th>
<th>Events per 100 000 Person-Years (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Women, No.</th>
<th>Person-Years ×10^6</th>
<th>Events, No.</th>
<th>Events per 100 000 Person-Years (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsiaa</td>
<td>9132</td>
<td>87</td>
<td>5</td>
<td>6.92 (3.93-12.2)</td>
<td>3.17 (1.29-7.80)</td>
<td>618 609</td>
<td>6317</td>
<td>4</td>
<td>6.33 (3.41-11.8)</td>
<td>2.58 (0.95-6.99)</td>
</tr>
<tr>
<td>Moderate preeclampsiaa</td>
<td>24 222</td>
<td>246</td>
<td>12</td>
<td>6.30 (4.43-8.96)</td>
<td>2.56 (1.41-4.66)</td>
<td>12 287</td>
<td>173</td>
<td>102</td>
<td>22.5 (14.9-33.8)</td>
<td>2.22 (1.47-3.36)</td>
</tr>
<tr>
<td>Gestational hypertensiona</td>
<td>9567</td>
<td>79</td>
<td>4</td>
<td>6.33 (3.41-11.8)</td>
<td>2.58 (0.95-6.99)</td>
<td>11 047</td>
<td>149</td>
<td>39</td>
<td>26.1 (13.1-35.7)</td>
<td>2.25 (1.63-3.09)</td>
</tr>
<tr>
<td>Normotensive pregnanciesb</td>
<td>15 325</td>
<td>231</td>
<td>40</td>
<td>7.17 (4.56-11.2)</td>
<td>3.09 (1.54-5.80)</td>
<td>823 872</td>
<td>11 615</td>
<td>1266</td>
<td>10.9 (6.3-11.6)</td>
<td>1.0 (Reference)</td>
</tr>
</tbody>
</table>

a Registration of a cardiomyopathy code (International Classification of Diseases, Revision 8 [ICD-8] code 425.99; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes I42.0-43.8 or O90.3) in the National Patient Register more than 5 months after a woman's first delivery in the study period. For women with only 1 delivery in the study period, follow-up extended from 5 months after the first delivery through subsequent pregnancies, until (1) a diagnosis of cardiomyopathy; (2) death; (3) emigration; (4) designated "missing"; or (5) December 31, 2012 (see the eFigure in the Supplement). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered.

b The main analyses included 1 075 763 women with 2 067 633 pregnancies. Note that the numbers of women reported in the table as contributing person-time to each exposure category sum to more than the total number of women included in the analyses because women with more than 1 pregnancy could contribute person-time to more than 1 exposure category.

Table 3. Hazard Ratios for Dilated Cardiomyopathy More Than 5 Months After First Delivery by History of Hypertensive Disorders of Pregnancy, Denmark, 1994-2012a,b

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Women, No.</th>
<th>Person-Years ×10^6</th>
<th>Events, No.</th>
<th>Events per 100 000 Person-Years (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsiaa</td>
<td>12 287</td>
<td>173</td>
<td>27</td>
<td>15.6 (10.7-22.7)</td>
<td>2.20 (1.50-3.33)</td>
</tr>
<tr>
<td>Moderate preeclampsiaa</td>
<td>40 258</td>
<td>697</td>
<td>102</td>
<td>14.6 (12.0-17.8)</td>
<td>1.89 (1.55-2.32)</td>
</tr>
<tr>
<td>Gestational hypertensiona</td>
<td>15 325</td>
<td>231</td>
<td>40</td>
<td>17.3 (12.7-23.6)</td>
<td>2.06 (1.50-2.82)</td>
</tr>
<tr>
<td>Normotensive pregnanciesb</td>
<td>1 023 770</td>
<td>18 212</td>
<td>1408</td>
<td>7.73 (7.34-8.15)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

a The analyses included 654 210 women; note that numbers of women reported in the table sum to more than the total number of women included in the analyses because women with more than 1 pregnancy could contribute person-time to more than 1 exposure category. For these analyses, follow-up began in 1994, the year in which International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes (in which subclassification of cardiomyopathy events was introduced) came into use in Denmark. For women with more than 1 delivery in the study period, follow-up extended from 5 months after the first delivery through subsequent pregnancies, until (1) a diagnosis of cardiomyopathy; (2) death; (3) emigration; (4) designated "missing"; or (5) December 31, 2012 (see the eFigure in the Supplement). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered. Similarly, follow-up for women who developed a form of cardiomyopathy other than dilated cardiomyopathy outside the peripartum period stopped at the time the cardiomyopathy diagnosis was registered (ie, women were censored if they developed another form of cardiomyopathy).

b Dilated cardiomyopathy more than 5 months after first delivery indicates registration of a dilated cardiomyopathy code (ICD-10 codes I42.0 or O90.3) in the National Patient Register more than 5 months after a woman's first delivery in the study period.

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Heart Association recommends monitoring for ischemic heart disease in 100,000 person-years. Accordingly, even though there was an association between HDP and increased risk of cardiomyopathy, the absolute risk was small. Although the American Heart Association recommends monitoring for ischemic heart disease following preeclampsia, a similar recommendation would not be justified for a more rare condition such as cardiomyopathy, regardless of the strength of the observed association with HDP. On the other hand, it seems prudent to suggest that physicians consider this association in the diagnostic workup of women with a history of HDP presenting with possible symptoms of heart failure.

**Discussion**

In this study, HDPs were associated with a lasting (>5 years postpartum) increase in risk of cardiomyopathy beyond the peripartum period, regardless of HDP severity. This increase in risk appeared to be independent of ischemic heart disease, the risk of which is increased among women with a history of preeclampsia, and approximately 50% of the risk was not associated with postgestational hypertension. The results suggest that links with HDP might be associated with a substantial proportion of idiopathic cardiomyopathy cases in women; in this cohort, 11% of all cardiomyopathy events in parous women occurred among women with a history of HDP.

However, cardiomyopathy events are rare, even among women in this study with a history of HDP (rates in women with a history of HDP, based on our data, were 14.6-17.3 cases/100,000 person-years). Accordingly, even though there was an association between HDP and increased risk of cardiomyopathy, the absolute risk was small. Although the American Heart Association recommends monitoring for ischemic heart disease following preeclampsia, a similar recommendation would not be justified for a more rare condition such as cardiomyopathy, regardless of the strength of the observed association with HDP. On the other hand, it seems prudent to suggest that physicians consider this association in the diagnostic workup of women with a history of HDP presenting with possible symptoms of heart failure.

**Table 4. Hazard Ratios for Cardiomyopathy More than 5 Months After First Delivery by History of Hypertensive Disorders of Pregnancy.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Women, No.</th>
<th>Person-Years ×10³</th>
<th>Events, No.</th>
<th>Events per 100,000 Person-Years (95% CI)</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia</td>
<td>12,279</td>
<td>171</td>
<td>25</td>
<td>14.7 (9.90-21.7)</td>
<td>2.38 (1.60-3.54)</td>
</tr>
<tr>
<td>Moderate preeclampsia</td>
<td>40,248</td>
<td>689</td>
<td>86</td>
<td>12.5 (10.1-15.4)</td>
<td>1.87 (1.50-2.34)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>15,318</td>
<td>228</td>
<td>30</td>
<td>13.1 (9.18-18.8)</td>
<td>1.83 (1.20-2.63)</td>
</tr>
<tr>
<td>Normotensive pregnancies</td>
<td>1,023,747</td>
<td>18,084</td>
<td>1,152</td>
<td>6.37 (6.01-6.75)</td>
<td>1 (Reference)</td>
</tr>
</tbody>
</table>

* For women with more than 1 delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until (1) cardiomyopathy diagnosis; (2) death; (3) emigration; (4) designated “missing”; or (5) December 31, 2012 (see the eFigure in the Supplement).

Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered. These analyses included women who reported in the table sum to more than the total number of women included in the analyses because women with more than 1 pregnancy could contribute person-time to more than 1 exposure category.

Cardiomyopathy more than 5 months after first delivery indicates registration of a cardiomyopathy code (International Classification of Diseases, Revision 8 [ICD-8] code 425.99; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes I42.0-43.8 or O90.3) in the National Patient Register more than 5 months after a woman’s first delivery in the study period.

Ischemic heart disease indicates registration of ICD-8 codes 410.09-414.99 or ICD-10 codes I20.0-25.9; 23,070 women developed ischemic heart disease during the study period. At the time they were diagnosed with ischemic heart disease, 242 had a history of severe preeclampsia, 1058 had a history of moderate preeclampsia, 331 had a history of gestational hypertension, and 21,439 had only had normotensive pregnancies. Follow-up for these women ended on the date the diagnosis was registered in the National Patient Register.

Diabetes indicates registration of ICD-8 codes 249.00-250.09 or ICD-10 codes E10.0-14.9; 19,040 women developed diabetes during the study period. At the time they were registered with diabetes in the National Patient Register, 343 had a history of severe preeclampsia, 1492 had a history of moderate preeclampsia, 485 had a history of gestational hypertension, and 16,720 had only had normotensive pregnancies.

Adjusted for maternal age, maternal birth year, parity, multiple pregnancy, stillbirth, and diabetes.

See Table 1 footnotes for ICD-8 and ICD-10 codes.

Women not registered with any of the above codes during pregnancy.

Shared underlying mechanisms could explain the association between HDP and cardiomyopathy. The pathological processes implicated in preeclampsia—angiogenic imbalance, complement activation, inflammation, hemodynamic changes—likely also contribute directly to cardiac stress exceeding that of normal pregnancy, producing overt cardiac damage in some women. Recent evidence of altered cardiac structure and function (predominantly left ventricular remodeling and diastolic dysfunction) during preeclamptic pregnancies and in the years immediately thereafter supports both this contention and the biological plausibility of the observed associations. Patten et al demonstrated that exposing mice to an excess of the antiangiogenic factor soluble fms-like tyrosine kinase-1 (sFlt1), levels of which are higher in women with preeclampsia, sFlt1 levels were correlated with hearts unable to withstand antiangiogenic insult. In women with preeclampsia, sFlt1 levels were correlated with cardiac diastolic dysfunction.

In women whose genetic make-up or lifestyle already renders them susceptible to cardiac disease, HDP may therefore provide an additional cardiac stressor, at which time the most severely affected women develop overt peripartum cardiomyopathy (which is characterized not just by diastolic dysfunction but by systolic dysfunction), while in other women, asymptomatic diastolic dysfunction may progress to heart failure, cardiomyopathy, or both over time. In women without pregestational cardiac susceptibility, cardiac diastolic dysfunction subsequent to HDP may increase susceptibility to later insults.

Because Melchiore et al also found the most severe and persistent cardiac dysfunction in women with preterm preeclampsia, and changes in antiangiogenic factor levels are more
marked in early preeclampsia, a stronger association for early preterm preeclampsia than for late preterm/term preeclampsia was expected, but this was not the case. However, in women who do not immediately develop peripartum cardiomyopathy, the risk of later cardiomyopathy may depend more on the ability to remodel cardiac damage, other cardiac risk factors, or the nature of the later postpregnancy cardiac stressors than on the degree of cardiac dysfunction or susceptibility at the end of pregnancy. Alternatively, the late preeclampsia group included many women with severe preeclampsia, which would have reduced the differences between the 2 preeclampsia groups.

Cardiomyopathy occurring after the peripartum period might be suspected simply to be unrecognized peripartum cardiomyopathy, the symptoms of which were ascribed to pregnancy or the aftermath of delivery. However, more than 80% percent of peripartum cardiomyopathy events in this cohort were diagnosed within 1 month of birth. Furthermore, the associations with cardiomyopathy persisted more than 5 years after an affected pregnancy, which argues for a distinct, persistent risk of cardiomyopathy outside the peripartum period.

Although treated as such in the primary analyses, cardiomyopathy is not a single entity, and the risk associated with HDP may apply only to specific cardiomyopathy subtypes. However, when the analyses were restricted to dilated cardiomyopathy, the results did not differ substantially, suggesting that the associations may primarily be driven by dilated cardiomyopathy.

The degree to which the findings in this study were related to unrecognized pregestational hypertension and chronic hypertension subsequent to HDP is critical to the interpretation of the results. Women with known pregestational hypertension were excluded from the study, but some of the women included in the cohort might have had unrecognized pregestational hypertension. However, bias from this source is unlikely, because similar associations between HDP and cardiomyopathy were observed for women with known or possible pregestational hypertension. Assuming that initiation of medication use is a good proxy for the postgestational development of chronic hypertension, mediation analysis results suggested that approximately 50% of the association between HDP and cardiomyopathy was associated with postgestational hypertension. However, the remaining 50% was not associated with hypertension and could be directly attributable to HDP (or an underlying common cause).

This study has several strengths and several potential limitations. Klemmensen et al validated HDP codes in the National Patient Register against the American Congress of Obstetricians and Gynecologists’ 2002 definitions and found that while the sensitivity of the register is moderate (69%) for preeclampsia (all types combined) and low (10%) for gestational hypertension, its specificity for HDP is very high (99%). Therefore, although not all HDP diagnoses are registered, those that are registered are likely correctly registered. Because of this high specificity, any bias attributable to misclassification of HDP-affected pregnancies as normotensive is most likely negligible. The register's low sensitivity for gestational hypertension is likely a consequence of the management of the condition by general practitioners, who do not report to the National Patient Register, and underreporting by hospital obstetricians of cases that do not warrant clinical intervention; in this study, women with gestational hypertension may have resembled women with moderate preeclampsia more than average women with gestational hypertension.

Cardiomyopathy diagnoses in the National Patient Register have not been validated. Because these diagnoses are only assigned following clinical workup, their specificity should be high. However, the register's sensitivity for cardiomyopathy may be low, because asymptomatic cardiomyopathy may go undetected or the condition may be mistaken for other conditions presenting with the same symptoms (eg, asthma, overweight, poor cardiovascular fitness). Parallel analyses of the associations between HDP and heart failure showed results consistent with those observed for cardiomyopathy, suggesting that some misclassification of cardiomyopathy as heart failure probably did occur but that this misclassification did not affect the conclusions regarding the strength and direction of the observed associations.

Adjustment for diabetes and smoking did not affect the results, suggesting that diabetes and smoking were not important confounders of the association between HDP and cardiomyopathy. In sensitivity analyses in which a woman's contribution to the study ended if she developed ischemic heart disease, the results did not change appreciably, suggesting that the relationship between HDP and cardiomyopathy was independent of ischemic heart disease, and any association of cardiovascular disease risk factors (eg, high cholesterol levels) with cardiomyopathy via ischemic heart disease likely did not explain the findings either. Adjusting for body mass index would have been valuable but was not possible, because only 9 years of follow-up including this variable were available.

Recent increases in awareness of the link between HDP and later ischemic heart disease could have resulted in heightened monitoring of, and increased detection of cardiomyopathy in, women with prior HDP. However, awareness of this link may not be common knowledge among physicians, as suggested by a single-institution study conducted in 2012-2013 despite the recent inclusion of previous preeclampsia as a risk factor for later ischemic heart disease in American Heart Association guidelines. Results of a sensitivity analysis that excluded years when surveillance was potentially heightened did not differ from the main results, making it unlikely that surveillance bias explained the results.

Conclusions

Women with a history of hypertensive disorders of pregnancy, compared with women without such a history, had a small but statistically significant increased risk of cardiomyopathy more than 5 months after delivery. Further research is necessary to understand whether there is a causal mechanism behind this association.
ARTICLE INFORMATION

Author Contributions: Drs Behrens and Boyd had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Behrens.

Critical revision of the manuscript for important intellectual content: Basit, Lykke, Ranthe, Wohlfahrt, Bundgaard, Melbye, Boyd.

Statistical analysis: Basit, Wohlfahrt.

Obtained funding: Behrens, Ranthe, Boyd.

Study supervision: Lykke, Ranthe, Wohlfahrt, Bundgaard, Melbye, Boyd.

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REFERENCES


