Prenatal Maternal Bereavement and Congenital Heart Defects in Offspring: A Registry-Based Study

WHAT’S KNOWN ON THIS SUBJECT: The etiology of congenital heart defects (CHDs) is largely unknown. A few studies have suggested that maternal emotional stress around the time of conception may be related to the occurrence of CHDs.

WHAT THIS STUDY ADDS: Using a large registry-based data source from Denmark, we found that prenatal exposure to maternal bereavement, as a marker of severe stress exposure, may increase the prevalence of CHDs in offspring.

abstract

OBJECTIVES: It has been suggested that maternal emotional stress during cardiogenesis may be a risk factor for congenital heart defects (CHD). We examined this association using bereavement around the time of conception as an indicator of maternal exposure to stress in a large registry-based study.

METHODS: We identified 1 770 878 singletons born in Denmark from January 1, 1978, to December 31, 2008. Of these, 44 820 children were born to mothers who had lost a first-degree relative during the time period from 1 year before their last menstrual period until delivery (6080 mothers lost a child or partner, and 38 740 mothers lost a parent or sibling). CHD diagnoses were identified from the Danish Registry of Congenital Heart Disease. We used logistic regression models to calculate prevalence odds ratios (ORs) of CHD for exposed children compared with unexposed children.

RESULTS: Exposed children had a slightly higher prevalence of CHD than unexposed children (0.94% vs 0.82%; adjusted OR = 1.11, 95% confidence interval 1.00–1.22). The association was most marked for children of mothers who had lost a child or partner (1.15% vs 0.82%; adjusted OR = 1.32, 1.04–1.67).

CONCLUSIONS: Prenatal exposure to severe emotional stress may slightly increase the prevalence of CHD in offspring. Pediatrics 2013;131:e1225–e1230
Congenital heart defects (CHD) are the most common congenital malformations, with a prevalence of ~5 to 10 per 1000 live births. They remain one of the leading causes of perinatal and infant mortality in many industrialized countries. The etiology of CHD is largely unknown, but the list of potential risk factors includes maternal exposure to stress around the time of conception. A case-control study conducted in Atlanta, Georgia, suggested that maternal stress related to job loss, divorce, separation, or death of a close friend or relative was associated with an increased risk of congenital heart defects. Two recent case-control studies based on the California Birth Monitoring Program in the United States found a similar association. A population-based study in Denmark reported that cranial-neural crest malformations were increased in offspring whose mothers were exposed to severe life events (ie, partner or child died or were hospitalized for cancer or acute myocardial infarction) during pregnancy. Some studies suggest that exogenous corticosteroid use during pregnancy poses a small increased risk of birth defects. Thus it is possible that increased production of corticosteroids in response to stress exposure may play a role.

The few previous studies had methodological problems (eg, small sample size, potential recall bias), and most have been restricted to cardiac outflow tract defects. In this study, we used data from national registries in Denmark to examine whether maternal bereavement around the time of conception, as a marker of severe stress exposure, was associated with CHDs in offspring.

METHODS

We conducted a national registry-based prevalence study in Denmark, using data from the Civil Registration System, the Medical Birth Registry, the Registry of Causes of Death, the Registry of Congenital Heart Disease, and the Integrated Database for Longitudinal Labor Market Research (IDA). All live-born children in Denmark are assigned a unique personal civil registration number (CPR number), which permits accurate linkage to all national registries. The Civil Registration System also provides a link between parents and their children. The Danish Data Protection Agency approved the study (j.nr. 2010-41-5375).

Study Population

We identified all singletons born in Denmark between January 1, 1978, and December 31, 2008, from the Medical Birth Registry and then used the Civil Registration System to identify their close relatives (mother, father, siblings, mother’s siblings, and mother’s parents). From a total of 1,866,660 singletons, we excluded 32,175 (1.7%) children with no information on their mother or father (almost all on fathers) and 62,631 (3.4%) children without information on gestational age. The proportion with no information on fathers was similar between children who were prenatally exposed to maternal bereavement (defined below) and children who were not. We also excluded 976 (0.1%) children whose older sibling or father died of CHD during the period from 1 year before their mother’s last menstrual period to the birth of the child. Thus, 1,770,878 singletons remained in the analysis.

Prenatal Exposure to Bereavement

We first classified offspring as exposed or unexposed based on whether their mother lost a close relative during the period from 1 year before her last menstrual period until delivery, a time period used in a previous study. Information on deaths was obtained from the Registry of Causes of Death. Exposed children were then categorized as (1) children of mothers who lost a child or partner and (2) children of mothers who lost a parent or sibling. We assumed that an event in the first category is more stressful than an event in the second category.

Up to 3 causes of death were recorded for each individual in the Registry of Causes of Death, based on the eighth revision of the International Classification of Diseases (ICD-8) from 1969 to 1993 and the 10th revision (ICD-10) since 1994. We also classified causes of death into 2 groups: (1) unexpected death (including sudden death without known causes [ICD-8 code 795; ICD-10 codes R65–R86]), motor vehicle accidents [ICD-8 codes 810–823; ICD-10 codes V01–V89], suicide [ICD-8 codes 950–959; ICD-10 codes X60–X84], and other accidents or violence [ICD-8 codes 800–807, 825–949, 960–999; ICD-10 codes V90–V99, W00–X59, X85–Y91] and (2) death from other causes. We classified the date of death as the date of exposure, although the associated stress would span a longer time period. We used gestational age and birth date to identify the first day of the mother’s last menstrual period (LMP), and then distinguished between 5 exposure periods: 12 to 7 months before LMP, 6 to 0 months before LMP, 0 to 13 weeks of pregnancy (first trimester), 14 to 27 weeks of pregnancy (second trimester), and 28 to 45 weeks of pregnancy (third trimester). In case of multiple exposures, we used the exposure date closest to the time of conception in the analysis.

Diagnoses of CHDs

Diagnoses of CHDs were obtained from the Registry of Congenital Heart Disease, which contains data on CHD from 1963 to the present. Since 1977, the registry has used hospital discharge diagnoses and outpatient visit diagnoses identified through the Danish Diagnosis...
National Registry of Patients (DNRP), with some exclusions (including patients diagnosed with an isolated atrial septal defect, a ventricular septal defect, or a patent ductus arteriosus before age 2 months, with no subsequent records of CHD in the DNRP, as well as patients with nonspecific CHD diagnoses). CHD diagnoses were coded according to ICD-8 until the end of 1993 and ICD-10 thereafter (ie, ICD-8 codes 746–747, except for 746.7, 746.9, and 747.5–747.9; and ICD-10 codes Q20–Q26, except for Q20.9, Q21.9, Q24.9, Q25.9, Q26.5–Q26.6, and Q26.9). Patients with >1 type of CHD were categorized according to their first CHD diagnosis, and only this diagnosis was included in the analysis.

Information on Potential Confounders
Information on gender, date of birth, maternal age, and parity was obtained from the Medical Birth Registry. This registry also provided data on maternal smoking status for the 1991 to 2007 period. History of CHD in parents and siblings was defined according to diagnoses in the Registry of Congenital Heart Disease. Information on maternal diabetes, defined as any type of diabetes diagnosed before the birth of the index child (ICD-8 codes 249-250, ICD-10 codes E10-E14 and Q24), was obtained from the DNRP. Maternal demographic and socioeconomic characteristics (place of residence, education, income, and cohabitation status) from 1980 on were obtained from the Integrated Database for Longitudinal Labor Market Research (IDA). Because we used maternal demographic and socioeconomic information from the year before the birth of the child, this information was available when children were born after 1981.

Statistical Analysis
We used logistic regression models to estimate prevalence odds ratios (ORs) with 95% confidence intervals for any CHD, comparing exposed children with unexposed children. In the logistic regression models, we also adjusted for gender (male, female), birth year (1978–1989, 1990–1999, 2000–2008), parity (0, 1, 2+), maternal age (<25, 25–29, 30–34, 35+ years), maternal diabetes (yes, no), parental history of CHD (yes, no), and siblings’ history of CHD (yes, no). To account for dependence between children of the same mother, we used the “cluster” option in the logistic models.

We conducted subanalyses restricted to children born after 1981. In these analyses we adjusted for several additional maternal covariates, including place of residence (capital city of Copenhagen and suburbs, cities with over 100,000 inhabitants, and other places), education (0–9, 10–11, 12+ years), income (quartiles in each calendar year), and cohabitation status (yes, no). Models restricted to children born from 1991 to 2007, when data on maternal smoking status was available, were also adjusted for this additional covariate. Finally, we took into account subtypes of CHD (including ventricular septal defects, atrial septal defects, and others).

RESULTS
Among 1,770,878 singletons, 44,820 children were exposed prenatally to maternal bereavement. In 6,080 cases, the mother lost a child or partner, and in 38,740 cases, the mother lost a parent or sibling. Bereaved mothers were older and had higher parity than mothers without a bereavement history (Table 1). Bereaved mothers were also more often smokers. The proportion of bereaved mothers was 2.2% during 1978–1989, 3.0% during 1990–1999, and 2.4% during 2000–2008. Overall, 14,507 (0.82%) children had CHD, with 26.5% diagnosed soon after birth and 72.9% within their first year of life. There was no difference between exposed and unexposed children in age at CHD diagnosis. The prevalence of CHD was 0.63% in

TABLE 1 Characteristics of Offspring Exposed and Unexposed to Maternal Bereavement, Denmark, 1978–2008

<table>
<thead>
<tr>
<th></th>
<th>Exposed Children</th>
<th>Unexposed Children</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>22,873 (51.0)</td>
<td>886,301 (51.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Girl</td>
<td>21,947 (49.0)</td>
<td>839,757 (48.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Birth year</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1978–1989</td>
<td>12,883 (28.8)</td>
<td>596,199 (34.0)</td>
<td></td>
</tr>
<tr>
<td>1989–1990</td>
<td>18,796 (41.9)</td>
<td>609,531 (35.3)</td>
<td></td>
</tr>
<tr>
<td>2000–2008</td>
<td>13,151 (29.3)</td>
<td>530,328 (30.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;25</td>
<td>8,145 (18.2)</td>
<td>372,134 (21.6)</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>15,649 (34.9)</td>
<td>657,384 (38.1)</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>14,190 (31.6)</td>
<td>496,350 (28.8)</td>
<td></td>
</tr>
<tr>
<td>35+</td>
<td>6,846 (15.3)</td>
<td>200,190 (11.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal parity</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0</td>
<td>16,848 (37.6)</td>
<td>783,524 (45.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17,869 (39.9)</td>
<td>656,922 (38.1)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>10,100 (22.5)</td>
<td>285,466 (16.5)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 (0.0)</td>
<td>146 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal diabetes</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHDs</td>
<td>634 (1.4)</td>
<td>20,224 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Siblings</td>
<td>865 (1.9)</td>
<td>20,335 (1.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parents</td>
<td>274 (0.6)</td>
<td>9571 (0.6)</td>
<td>.11</td>
</tr>
</tbody>
</table>
children born during 1978–1989, 0.92% in those born during 1990–1999, and 0.91% in those born during 2000–2008. Exposed children had a slightly higher prevalence of CHD than unexposed children, especially for children of mothers who had lost a child or partner (Table 2). An increased prevalence of CHD was observed in children of mothers whose older child or partner died of an expected cause but not of an unexpected cause.

Maternal exposure to bereavement during the period from 6 months before the LMP through the second trimester of pregnancy tended to be associated with a slightly increased prevalence of CHD (Table 3). Because of small numbers, it was not meaningful to stratify these analyses by type of loss, cause of death, and exposure period.

We obtained similar results when we restricted the analysis to children born after 1981 and additionally adjusted for maternal place of residence, education, income, and cohabitation status and when we restricted analyses to children born from 1991 to 2007 and further adjusted for maternal smoking (data not shown).

Ventricular septal defects and atrial septal defects were the 2 most frequent heart malformations (n = 3456 [23.8%] and n = 2426 [16.7%], respectively). Analyses stratified by CHD subtypes suggested that the association between CHD and mother’s exposure to bereavement was not limited to any specific CHD. But information on individual subtypes of CHD was sparse (data not shown).

**DISCUSSION**

We found that women exposed to severe emotional stress from bereavement gave birth to children with a slightly increased prevalence of CHD. The increase tended to be greater in children of mothers who lost an older child or partner around the time of conception.

Our finding of increased prevalence of CHD among children prenatally exposed to maternal bereavement agrees with the few studies published on this topic. The larger increase in the prevalence of CHD in children of mothers who lost an older child or partner is consistent with our expectation and with the results of a previous Danish study showing that death of an older child was associated with a higher risk of cranial-neural-crest malformations in subsequent offspring.

We expected the association between maternal stress and CHD to be stronger for unexpected deaths than for deaths due to other causes, but we found that mothers who lost a child or partner after an illness gave birth to children with a higher prevalence of CHD, compared with mothers who lost an older child or partner due to unexpected causes. Chance could explain this because the numbers of CHD cases are small, especially for unexpected causes, or the stress exposure may actually be greater for those who anticipate the course of a fatal disease. As expected, we saw an increased prevalence of CHD in children of mothers who lost a close relative during the period from 6 months before their last menstrual period through the second trimester.

Our study has a number of strengths. First, it is a large population-based study using data from national registries, thus mitigating recall bias or selection bias due to nonparticipation or loss to follow-up. Second, we used bereavement as a marker of severe emotional stress. Bereavement is more universally perceived as stressful than other measurable indicators of stress, regardless of personality, ability to cope, self-confidence, and social support. Third, data on CHD diagnoses were obtained from the Registry of Congenital Heart Disease, which uses hospital diagnoses identified through

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**TABLE 2** Prevalence ORs for CHDs According to Maternal Exposure to the Death of a Close Relative, Denmark, 1978–2008

<table>
<thead>
<tr>
<th>No. of Children</th>
<th>No. (%) With CHD</th>
<th>Crude OR</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed children</td>
<td>1 726 058</td>
<td>14 087 (0.82)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Exposed children</td>
<td>44 820</td>
<td>420 (0.94)</td>
<td>1.15</td>
<td>1.11 (1.00–1.22)</td>
</tr>
<tr>
<td>Death of mother’s older child or partner</td>
<td>6080</td>
<td>70 (1.15)</td>
<td>1.42</td>
<td>1.32 (1.04–1.67)</td>
</tr>
<tr>
<td>Unexpected death</td>
<td>1666</td>
<td>11 (0.66)</td>
<td>0.81</td>
<td>0.84 (0.46–1.51)</td>
</tr>
<tr>
<td>Other death</td>
<td>4356</td>
<td>58 (1.33)</td>
<td>1.64</td>
<td>1.47 (1.13–1.91)</td>
</tr>
<tr>
<td>Death of mother’s sibling or parent</td>
<td>38 740</td>
<td>350 (0.90)</td>
<td>1.11</td>
<td>1.07 (0.96–1.19)</td>
</tr>
<tr>
<td>Unexpected death</td>
<td>4254</td>
<td>46 (1.08)</td>
<td>1.33</td>
<td>1.32 (0.99–1.77)</td>
</tr>
<tr>
<td>Other death</td>
<td>34 150</td>
<td>302 (0.88)</td>
<td>1.08</td>
<td>1.05 (0.93–1.17)</td>
</tr>
</tbody>
</table>

The logistic regression was adjusted for gender, birth year, parity, maternal age, maternal diabetes, parental history of CHD, and siblings’ history of CHD. The reference group was unexposed children. CI, confidence interval.

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**TABLE 3** Prevalence ORs for CHDs According to Timing of Maternal Loss of a Close Relative, Denmark, 1978–2008

<table>
<thead>
<tr>
<th>No. of Children</th>
<th>No. (%) With CHD</th>
<th>Crude OR</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed children</td>
<td>7–12 mo before LMP</td>
<td>13 000</td>
<td>101 (0.78)</td>
<td>0.95</td>
</tr>
<tr>
<td>0–6 mo before LMP</td>
<td>14 124</td>
<td>139 (0.98)</td>
<td>1.21</td>
<td>1.17 (0.99–1.38)</td>
</tr>
<tr>
<td>First trimester</td>
<td>6174</td>
<td>64 (1.04)</td>
<td>1.27</td>
<td>1.23 (0.96–1.57)</td>
</tr>
<tr>
<td>Second trimester</td>
<td>6256</td>
<td>67 (1.07)</td>
<td>1.32</td>
<td>1.26 (0.99–1.61)</td>
</tr>
<tr>
<td>Third trimester</td>
<td>5266</td>
<td>49 (0.93)</td>
<td>1.14</td>
<td>1.11 (0.84–1.48)</td>
</tr>
</tbody>
</table>

The logistic regression was adjusted for gender, birth year, parity, maternal age, maternal diabetes, parental history of CHD, and siblings’ history of CHD. The reference group was unexposed children. CI, confidence interval.
the DNRP. In addition, specific exclusions were made to increase specificity. Validation studies, comparing CHD diagnoses recorded in the DNRP with clinical records, have shown an overall positive predictive value of 89% to 90%.21,22 The overall CHD prevalence in our study is comparable to the reported prevalence of 7 to 8 per 1000 live births in Denmark and in Europe.1,2,22 The time trend showing that the prevalence increased in the 1980s and stabilized afterward is also consistent with the literature.23 An additional strength was our ability to adjust for a number of potential confounders, especially socioeconomic conditions.

The study also has limitations. First, although our study population included the entire population of children in Denmark born in a period spanning 3 decades, the number of CHD cases among exposed children remained rather small. This was particularly true for more detailed exposure categories. Our ability to examine individual types of CHD was also limited. Second, the timing of stress is difficult to define accurately, especially for deaths due to causes other than sudden unexpected death, because stress may have commenced and been more severe before the event of death. Third, we included only live-born children, excluding spontaneous or induced abortions. If stress induces severe heart malformations that lead to spontaneous or induced abortion, we would have underestimated the association. At the same time, if death of an older child means that subsequent problem pregnancies are less likely to be terminated, we may have overestimated the association. Still, prenatal screening became common only in the latest part of the study period.24 Fourth, we cannot rule out that the associations we found may be due to changes in behavior (eg, smoking, drinking, diet, sleep) under stress instead of increased exposure to stress hormones, because we had only limited information on maternal smoking and no information on other lifestyle factors. Finally, we did not include other, more common but often less stressful conditions, such as job loss, divorce, and serious illness of relatives. We also lacked information on mothers’ social support networks, which may be important in buffering the stress response.25

Findings in our study, together with those of others,2–10 support the hypothesis that prenatal exposure to severe stress is associated with a slightly increased prevalence of CHD in children. The overwhelming feelings of grief, anger, and dismay26,27 in pregnant women could adversely affect unborn children in many ways, which calls for support and care. Health professionals should be prepared to help bereaved women cope with this serious life event. For future studies, the biological mechanisms through which maternal stress causes CHD need to be elucidated. Data on ways of coping and changes in behavior should also be recorded, which will not only provide information on mechanisms but also on possible prevention and intervention.

REFERENCES

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