Maternal death in women with epilepsy
Smaller scope studies

Jakob Christensen, PhD, Claus Vestergaard, MSci, and Bodil Hammer Bech, PhD

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Abstract

Objective
To determine the maternal mortality in women with epilepsy.

Methods
This was a matched case-control study of pregnant women in Denmark who were born in Denmark between January 1, 1962, and December 31, 1994, and who were alive on their 18th birthday. We defined maternal mortality as deaths in pregnancy and the first 42 days after termination of pregnancy. Cases were pregnancies in women with a diagnosis of epilepsy before the termination of pregnancy. Data were analyzed with a conditional logistic model. For comparison, we estimated the mortality in women of childbearing age (18–50 years) diagnosed with epilepsy regardless of pregnancy status using a Poisson model.

Results
We identified 2,105,084 pregnancies, including 11,976 (0.57%) pregnancies in which the mother was diagnosed with epilepsy. Of the 176 maternal deaths in this cohort, 5 women had a diagnosis of epilepsy. The mortality associated with an epilepsy diagnosis was >5 times higher compared to the mortality in women without this diagnosis (odds ratio 5.57, 95% confidence interval 2.23–13.9, \( p < 0.001 \)).

Conclusions and Relevance
Maternal mortality in women with epilepsy in Denmark was lower than what has previously been reported from United States and the United Kingdom. However, the maternal mortality in women with epilepsy was considerably higher compared to women without epilepsy. Further studies should address whether improving epilepsy care in women with epilepsy could reduce the rate of maternal deaths.
The overall mortality in young people with epilepsy is increased compared with persons without epilepsy. Recent studies suggest that the mortality in the subset of women with epilepsy who are pregnant is also very high. A report from the United Kingdom found that 1 in 1,000 pregnant women with epilepsy died during or shortly after pregnancy. A study from the United States suggests that women with epilepsy are at considerable risk during delivery, with a >10-fold increased risk of death. Because of these alarming mortality figures during pregnancy and delivery, we aimed to study whether these figures could be replicated among Danish women with epilepsy. In addition, because women with epilepsy who are not pregnant also have an increased mortality, we estimated the overall mortality in women with epilepsy of childbearing age regardless of pregnancy status.

Methods

From the Danish Central Register, we identified all women born in Denmark between January 1, 1962, and December 31, 1994, who were alive on their 18th birthday.

From the Danish National Hospital Register, we obtained information on all admissions (from 1977) and outpatient contacts (from 1995) with an epilepsy diagnosis (ICD-8 code 345, ICD-10 codes DG40 and DG41) recorded before December 31, 2013. From the same register, we identified all pregnancy-related admissions (from 1977) and outpatient contacts (from 1995) recorded before December 31, 2013 (ICD-8 codes 630–678, ICD-10 codes DO or DZ32–DZ37).

Cases were defined with the World Health Organization definition of maternal death as the death of a woman while pregnant or within 42 days of termination of pregnancy. However, some pregnancy-related contacts had unknown results; i.e., neither abortion nor birth was registered. This may be due to loss to follow-up (e.g., emigration) or because the woman died while pregnant. In these cases, we checked to see if the mother died within 40 weeks of the first day of the last menstrual period, which was estimated from the gestational age registered in the Danish National Hospital Register by subtracting the gestational age from the date of admission. We excluded all pregnancies with an estimated day of the last menstrual period after December 31, 2012, to ensure complete follow-up of any pregnancy. If no gestational age and outcome (abortion or birth) were recorded, we recorded it as maternal death if the mother died within 42 days of last recorded pregnancy-related admission plus 15 weeks, assuming that this would be an average duration of pregnancy after a hospital admission. To check the influence of this assumption on the mortality estimate, we estimated mortality assuming a duration of pregnancy of 10, 15, 20, 30, and 40 weeks after the last pregnancy-related admission.

For each maternal death, the pregnancy was matched with pregnancies that did not result in death. The pregnancies were matched on yearly income the year before termination of the pregnancy (1st–3rd, 4th–7th, and 8th–10th deciles), calendar year (1-year intervals), parity, and maternal age (±365 days). Because of the rarity of both epilepsy and death, up to 100 control pregnancies were chosen. Data were analyzed with a conditional logistic model with the diagnosis of epilepsy before the termination of pregnancy as the exposure.

We estimated the mortality in women of childbearing age (age 18–50 years) diagnosed with epilepsy within the previous 5 years regardless of pregnancy status. Women were followed up from their 18th birthday or January 1, 2000, whichever came last, until the date of death/emigration or December 31, 2013, whichever came first. Relative mortality rates aggregated over 2-year periods were calculated with a Poisson model adjusted for income, calendar year, and parity.

Standard protocol approvals, registrations, and patient consents

The study includes only anonymous data, which by Danish law does not require ethics review board approval. However, the study was approved by the Danish Data Protection Agency (No. 2013-41-1719).

Data availability

Data not provided in the article because of space limitations cannot be shared for legal or ethical reasons, but summary data will be shared by request from any qualified investigator if in accordance with the Danish law.

Table 1 Cause of maternal death in 207 women who died in Denmark between January 1, 1977, and December 31, 2013

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accident</td>
<td>35</td>
<td>16.9</td>
</tr>
<tr>
<td>Violent death</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Suicide</td>
<td>17</td>
<td>8.2</td>
</tr>
<tr>
<td>Natural death</td>
<td>138</td>
<td>66.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>6.8</td>
</tr>
<tr>
<td>Total</td>
<td>207</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Glossary

ICD-8 = International Classification of Diseases, 8th revision; ICD-10 = International Classification of Diseases, 10th revision.
Results

We identified 2,105,084 pregnancies among 801,739 women. The outcomes of the pregnancies were as follows: 1,364,733 (64.8%) births, 584,757 (27.8%) abortions, and 155,594 (7.4%) with no recorded outcome. Among all the pregnancies, 11,976 (0.57%) occurred in women diagnosed with epilepsy (7,196 [60.1%] resulted in birth, 3,868 [32.3%] resulted in abortion, and 912 [7.6%] had no recorded outcome).

In the main analysis, we assessed the mortality assuming that the end of pregnancy in women with no recorded outcome was 15 weeks after the last pregnancy admission. Of the 176 maternal deaths in this cohort, 5 had a diagnosis of epilepsy within 5 years.

The maternal mortality associated with an epilepsy diagnosis was increased >5-fold compared to the mortality in women without this diagnosis (odds ratio 5.57, 95% confidence interval 2.23–13.9, p < 0.001). The causes of death among the 207 maternal deaths are shown in table 1.

We performed secondary analyses assuming varying lengths of pregnancy for pregnancies with no reported outcome. The relative maternal mortality increased with assumed length of pregnancy in weeks after last pregnancy-related admission with unknown outcome (table 2). Among the 207 maternal deaths, the mean age at time of death was 29.4 years (SD 5.4, range 18–43 years); the parity was first delivery (n = 75), second delivery (n = 60), third delivery (n = 34), fourth delivery (n = 23), and fifth or more deliveries (n = 15); and the income deciles were 1st to 3rd decile (n = 55), 4th to 7th decile (n = 111), and 8th to 10th decile (n = 41).

We also estimated the overall mortality in women of childbearing age (18–50 years of age) regardless of pregnancy. In the years 2000 to 2013, the prevalence of epilepsy was 0.41% for women 18 to 50 years of age. For women of childbearing age, the mortality was ≈15 times higher in women diagnosed with epilepsy within 5 years compared to women without epilepsy (figure 1). There were no obvious time trends in the mortality in women of childbearing age (figure 2). The causes of death among the women of childbearing age (18–50 years of age) who died in Denmark in the years 2000 to 2013 are shown in table 3.

| Assumed length of pregnancy after last pregnancy-related admission with no reported outcome | Pregnan
cies without epilepsy, n | Maternal deaths without epilepsy, n | Pregnan
cies with epilepsy, n | Maternal deaths with epilepsy, n | OR* (95% CI) | p Value |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>10 wk + 42 d</td>
<td>16,438</td>
<td>165</td>
<td>94</td>
<td>5</td>
<td>5.60 (2.23–14.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15 wk + 42 d</td>
<td>17,013</td>
<td>171</td>
<td>94</td>
<td>5</td>
<td>5.57 (2.23–13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20 wk + 42 d</td>
<td>17,707</td>
<td>177</td>
<td>107</td>
<td>6</td>
<td>5.95 (2.57–13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30 wk + 42 d</td>
<td>18,737</td>
<td>187</td>
<td>107</td>
<td>7</td>
<td>7.04 (3.22–15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40 wk + 42 d</td>
<td>20,026</td>
<td>200</td>
<td>121</td>
<td>7</td>
<td>6.19 (2.84–13.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; OR = odds ratio.

*The pregnancies were matched on yearly income the year before termination of the pregnancy, calendar year, parity, and maternal age.
Discussion

In this study of >2 million pregnancies, including >11,000 pregnancies in women with epilepsy, 5 women with epilepsy died (41.7 deaths per 100,000 pregnancies in women with epilepsy compared to 8.2 deaths per 100,000 pregnancies in women without epilepsy). Although the maternal mortality was highly increased in Danish women with epilepsy, the estimated mortality is lower than what was reported from the United Kingdom, i.e., a mortality rate in women with epilepsy of 100 deaths per 100,000 maternities compared to the overall maternal mortality in United Kingdom, which was estimated at 11 deaths per 100,000 maternities. Although our study was not confined to delivery, our mortality estimates are also lower than what was estimated during delivery in a study from the United States that reported a mortality rate in women with epilepsy of 80 per 100,000 compared to a mortality rate of 6 per 100,000 pregnancies in women without epilepsy.4

There may be a number or reasons for the discrepancies between the studies on maternal mortality. We used data from the entire Danish population, which ensures updated registration of participant’s vital status, allowing little room for bias due to loss to follow up. The frequency of women with epilepsy among the pregnant women (0.57%) was similar to what has been reported previously; pregnancies in women with epilepsy usually are reported to make up 0.3% to 0.6% of all pregnancies.7 Pregnant women seem less likely to die of natural causes compared to women of childbearing age (tables 1 and 3). A possible reason is that women with underlying severe disorders seldom become pregnant. There were too few maternal deaths in women with epilepsy to allow assessment of cause of death. In the most recent report from the United Kingdom on maternal mortality, sudden unexplained death in epilepsy was reported to be the most frequent cause of death, found in 12 of 14 deaths (86%) in pregnant women with epilepsy.8 The most important risk factor for sudden unexplained death in epilepsy is generalized tonic-clonic seizures, but it is not possible to retrieve information on seizure type and frequency from the Danish National Hospital Register.

About 7% of the pregnancy hospital contacts were not followed by abortion or birth; therefore, we had to rely on an estimation of the length of the pregnancy after this pregnancy-related contact. When the length of follow-up was increased, the mortality estimates associated with epilepsy also increased. However, the overall mortality in women with epilepsy regardless of pregnancy status is increased to a much larger extent (figure 1), suggesting that women with epilepsy who become pregnant may be much healthier than women with epilepsy in general.

We confirm previous results showing a higher risk of maternal death in women with epilepsy compared to women without epilepsy. Further studies should address whether improving epilepsy care in women with epilepsy could reduce the increased rate of maternal deaths.5

Author contributions
All authors contributed to the conception and design of the study and to the interpretation of the data and analyses. Claus Vestergaard analyzed the data and performed the statistical analysis. Jakob Christensen drafted the article. All authors provided critical revision for important intellectual content.
and approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work.

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Disclosure
J. Christensen received honoraria from serving on the scientific advisory board of UCB Nordic and Eisai AB, received honoraria from giving lectures from UCB Nordic and Eisai AB, and received funding for a trip from UCB Nordic. C. Vestergaard and B. Bech report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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References
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