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Arch Dis Child Fetal Neonatal Ed 2009 94: F105-F110 originally published online November 10, 2008
doi: 10.1136/adc.2007.135459

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Risk of stillbirth and neonatal death linked with maternal mental illness: a national cohort study

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ABSTRACT

Background: Babies of mothers with psychotic disorders are known to have higher rates of poor obstetric outcome, including higher mortality rates.

Objective: To estimate risks of stillbirth and neonatal death by specific causes in babies of mothers with histories of severe mental illness, relative to the general population.

Methods: A cohort of 1.45 million live births and 7021 stillbirths during 1973–98 was identified from Danish national registers. These registers were linked to identify babies who were stillborn or died neonatally after exposure to maternal psychiatric illness.

Results: Risks of stillbirth and neonatal death were raised for virtually all causes of death for all of the maternal psychiatric diagnostic categories. For most causes of death, offspring of women with schizophrenia and related disorders had no greater risks of stillbirth or neonatal death than offspring of women with other maternal psychiatric disorders (eg, neonatal death (NND) due to immaturity: relative risks (95% CI) schizophrenia and related disorders: 1.1 (0.4 to 3.5), affective disorders: 2.0 (1.2 to 3.5)). There was a greater risk of fatal congenital malformation associated with a history of maternal affective disorder (stillbirth 2.4 (1.1 to 5.1), NND 2.1 (1.4 to 3.3)) or schizophrenia and related disorders (stillbirth 2.4 (0.8 to 7.6), NND 2.2 (1.1 to 4.1)) than with maternal alcohol/drug-related disorders (stillbirth 1.2 (0.4 to 3.8), NND 1.1 (0.6 to 2.2)).

Conclusions: Higher risk of perinatal loss may be linked to factors associated with maternal psychiatric illness in general, such as insufficient attendance for antenatal care and unhealthy lifestyles rather than the maternal mental illness itself.

Raised risks of perinatal death in babies of women with psychiatric illness have been found in a number of studies.1–4 Gaining a greater understanding of these risks is an important public health concern, especially since increasing numbers of mentally ill women now become pregnant.5 Previous research has found raised risks of perinatal death associated with maternal schizophrenia,1–3 maternal psychotic disorder4 and parental schizophrenia,2,6,7 and raised risks of stillbirth among women with affective or substance-related disorders in the general US population.6 Our research has suggested that higher risks of neonatal death are associated with maternal affective or alcohol/drug-related disorders than with maternal schizophrenia and related disorders.8 Several studies have found no evidence of raised risks for either stillbirth or neonatal death in the offspring of women with either schizophrenia,9 bipolar or unipolar disorders8 or affective psychosis adjusted for a range of factors including maternal smoking history.10 The psychiatric journals have tended to concentrate on associations between psychiatric diagnoses (especially schizophrenia) and poor birth outcomes: Bennedsen et al found raised risks of congenital malformations in babies of women with schizophrenia in Denmark,11 but paediatric publications have focused on the effects of drug and alcohol misuse on birth outcomes. Many studies have identified maternal substance abuse during pregnancy as a risk factor for a range of poor birth outcomes such as congenital malformations of varying type and severity, prematurity and perinatal death.12–15

In this study we aimed to examine a range of specific causes of perinatal death in babies of women with psychiatric inpatient histories, including substance-related disorders. We examined the problem of rarity of exposure (severe maternal mental illness) and rarity of outcome (perinatal death) by using data from the large population registers available in Denmark.

METHODS

Study cohort

We identified all live and stillbirths between 1 January 1973 and 31 December 1998 using data from the Danish Civil Registration System.16 Each Danish resident is assigned a unique number which may be used to link information about the
individual between different registers to a high degree of completeness. We used the Central Population Register containing the date of birth, death and emigration of each person living in Denmark, the Psychiatric Central Register recording diagnoses for all psychiatric inpatient admissions since 1969, the Cause of Death Register and the Medical Births Register, which record the cause of death or stillbirth, respectively, since 1973. The International Classification of Diseases (ICD) 8th revision was used from 1 January 1973 to 31 December 1993 and the 10th revision thereafter. We used 1 January 1973 as the study entry date because the Medical Births Register was computerised from that date. Causes of stillbirth were not recorded in the Medical Births Register after 31 December 1996. A stillbirth is recorded in Denmark when the fetus is lost at 28 weeks’ gestation or later. A neonatal death is one that occurs during the first 28 days of life.

We restricted our cohort to singleton births since observations from multiple birth sets are not statistically independent. We identified 7021 stillbirths between 1 January 1973 and 31 December 1996, and 1 450 329 live births between 1 January 1973 and 31 December 1998.

Exposure status and maternal psychiatric admission
Babies were “exposed” to maternal mental illness if their mother was admitted to hospital with any psychiatric illness (or specific diagnostic category) before the offspring date of birth (live or stillborn). Diagnoses of maternal mental illness were categorised using ICD-8 and ICD-10 codes below; we included all admissions for psychiatric disorders in women aged 16 years and over. These groups of codes were selected for reasons of clinical relevance, and have been used in other Danish registry studies.

- Schizophrenia and related disorders: (schizophrenia, schizoaffective disorders) ICD-8: 295, 296.8, 297, 298.59, 301.83; ICD-10: F20–F29.

Cause-of-death classifications
We classified causes of death according to the ICD codes for the primary cause of stillbirth or neonatal death that were recorded in the national registers. The ICD-8 and ICD-10 codes used in each category of stillbirth and neonatal death are shown in the Appendix, table A1. These codes were selected by an obstetrician (Dr Louise Kenny; see “Acknowledgements”) on the basis of clinical relevance.

Modelling
We used Poisson regression (STATA, version 8.0) to estimate relative risks of mortality in the offspring of mothers previously admitted with mental illness, compared with unexposed offspring. We compared the cause-specific stillbirth rates and neonatal mortality in exposed versus unexposed populations, with relative risks estimated as risk ratios. The risk of stillbirth was calculated as the number of deaths divided by the number of live and stillbirths; risk of neonatal death was the number of deaths over the number of live births. Using Poisson models these risk ratios were adjusted for 5-year period bands. We additionally adjusted for maternal age at birth for stillbirths, and maternal age at birth, birth order and offspring sex for live births (these additional adjustments made no material difference to the effect and variance estimates, and so these results are not included in this paper).

A previous study using the same dataset to 1993 estimated relative risks of stillbirth and neonatal death using generalising estimating equation methods to take account of familial clustering effects. Since most perinatal deaths occurred during the early part of the period, and the previous study found little difference between results using this method and those that made no such adjustment, we chose not to use methods which account for within-family correlation. This decision was further supported by prior validation work conducted by one of this study’s coauthors (RTW) using the same study cohort we report in this paper.

RESULTS
Stillbirths
Of the 7021 stillbirths, 188 were exposed to a history of any maternal psychiatric admission before birth. Of these mothers,
19 had been admitted for schizophrenia and related disorders, 47 for affective disorders and 38 for alcohol/drug-related disorders. Figure 1 and supplementary table 1 (online only) show the relative risks of cause-specific stillbirth linked with maternal admission for specific psychiatric disorders, compared with the general population.

The risks of stillbirth are raised for each of the causes of death for all of the maternal psychiatric diagnostic categories. Some of the relative risks are more than twofold but we found no pattern of raised risks by either cause of stillbirth or maternal diagnostic category. Maternal psychiatric history of alcohol/drug-related disorder is associated with a greater than twofold increased risk of stillbirth due to complications of delivery (relative risk (RR) = 2.3, 95% confidence interval (CI) 1.2 to 4.2) and similar raised risks for stillbirth due to congenital malformations of the fetus in women with histories of affective disorders (RR = 2.4, 95% CI 1.1 to 5.1). Non-significant raised risks were seen in women with schizophrenia and related disorders, where there were only three women in the exposed group (RR = 2.4, 95% CI 0.8 to 7.6, n = 3). “All other causes of stillbirth” include those due to injury to the mother or due to maternal illness. We found sevenfold and twofold raised risks, respectively, for these causes of death (injury to mother: RR = 7.5, 95% CI 2.9 to 19.0, n = 5; maternal illness: RR = 2.5, 95% CI 1.3 to 4.8, n = 10).

Neonatal deaths

Of the 6646 neonatal deaths, 201 were of offspring of mothers who were previously admitted for any psychiatric illness (22 with maternal schizophrenia and related disorders, 66 with maternal affective disorders and 55 with maternal alcohol/drug-related disorders). Figure 2 and supplementary table 2 (online only) show the relative risks of cause-specific neonatal death linked with history of maternal admission for specific psychiatric disorders, compared with the general population.

The relative risk of each cause of neonatal death for each type of maternal psychiatric history was raised, with one exception. This was neonatal death due to anoxia and birth injury to the infant brain in children of women with histories of schizophrenia and related disorders (RR = 0.9, 95% CI 0.2 to 3.7). Compared with the general population, a maternal history of alcohol/drug-related disorder was associated with a greater than threefold raised risk of both neonatal death due to anoxia and birth injury to the brain (RR = 3.4, 95% CI 2.1 to 5.6), and “other conditions originating in the perinatal period” (RR = 3.8, 95% CI 2.1 to 6.9). We found greater than doubled risks of neonatal death in babies of women with histories of affective disorders for death due to anoxia and birth injury to the brain (RR = 2.6, 95% CI 1.6 to 4.3), “other conditions originating in the perinatal period” (RR = 2.3, 95% CI 1.2 to 4.7) and congenital malformations (RR = 2.1, 95% CI 1.4 to 3.3). A history of schizophrenia and related disorders is associated with greater than doubled risks of neonatal death due to congenital malformations compared with the general population (RR = 2.2, 95% CI 1.1 to 4.1).

Similarities between risks of stillbirth and neonatal death

Across the maternal diagnostic categories, there were similar patterns of relative risks between stillbirth and neonatal death from congenital malformations, and between stillbirth due to complications of delivery, which include anoxia and birth injury to the brain, and neonatal death as a result of anoxia and birth injury to the brain.

DISCUSSION

Main findings

We observed raised risks of stillbirth and neonatal death for each cause of death and for all maternal psychiatric histories, with only one exception. In addition, we did not find higher risks of stillbirth or neonatal death in babies of women with schizophrenia and related disorders compared with the other psychiatric disorders. A markedly raised risk of stillbirth after injury to the mother was indicated amongst women with any psychiatric admission history, compared with the general population, but this result was based on just five deaths in the exposed population. A history of maternal schizophrenia and related disorder or maternal affective disorder was found to be a greater risk factor for perinatal death due to congenital malformation than maternal history of substance-related...
disorders. Our results are consistent with previous studies reporting raised risks of stillbirth and neonatal death in offspring of women with schizophrenia.\(^1\)

**Strengths and limitations**

Data were collected prospectively over a 26-year period and are based on the whole population of Denmark, allowing us to examine cause-specific outcomes for a range of mental illnesses. A limitation is that we examined offspring outcomes for mothers with a history of inpatient admission for severe psychiatric illness, so our results possibly cannot be generalised to those with less serious mental illness. For this investigation we had no data to examine whether mothers smoked, drank alcohol or took illicit drugs during pregnancy, and no measures of socioeconomic status. Prescription of psychotropic drugs, mothers’ physical health status in pregnancy and antenatal care attendance record were also not available from the study registers.

Bennedsen et al found comparable point estimates of relative risk of all-cause stillbirth and neonatal death associated with maternal schizophrenia using the same data from the Danish registers over a shorter time period.\(^11\) Our study reports relative risks associated with the wider diagnostic range of maternal schizophrenia and related disorders and over a longer time period, increasing the power of the study.

Since psychiatric data begin from 1969, only the previous 4 years of psychiatric history were known for women who gave birth in 1973, whereas the psychiatric history of women giving birth in later years was known for a much longer time period. However, any underascertainment of maternal mental illness in the earlier years would tend to underestimate relative risks in this period and overall. The number of beds available for psychiatric patients has decreased since the 1970s.\(^24\) The perinatal mortality rate has also fallen; in our birth cohort there was an approximate 20% fall in the stillbirth rate between the early 1970s and late 1990s, while the neonatal death rate fell by more than 50%. This study allowed for these cohort effects in its design by adjusting for period as a covariate.

**Timing of psychiatric illness and perinatal death**

This study limited stillbirths and neonatal deaths in the exposed population to those that occurred at some time after an admission for psychiatric illness, in order to prevent reverse causality bias.\(^23\) We thereby aimed to estimate risks associated with known serious mental illness before death, and specifically to exclude mental illness that may in part have been precipitated by the loss of a child. Using national Danish registry data, Li et al reported raised risks of maternal psychiatric hospitalisation in these circumstances.\(^26\)

**Poor lifestyle choices and antenatal care**

The general nature of the raised risks seen across all maternal disorder categories suggests the involvement of risk factors related to the psychiatric population itself, rather than to specific diagnostic groups. Likely contributory factors to these raised risks in this population include poor lifestyle choices such as antenatal smoking and drinking,\(^27\)\(^28\) and the relatively low socioeconomic status of many people with mental health problems.\(^29\)

Raised risks due to complications of delivery, anoxia and birth injury to the infant brain may be related to poor uptake of prenatal care in some sections of the psychiatric population. Previous research in the USA has identified psychiatric illness and substance abuse as a risk factor for receiving inadequate antenatal care\(^30\) and other research indicates that late booking and fewer antenatal visits increase the incidence of babies born with low or very low birth weight or preterm birth.\(^39\) Conversely, perhaps greater care is taken with women with schizophrenia and similar disorders, illnesses that are regarded as particularly serious. We had no information about the nature of the injuries of the women who lost babies owing to injury to the mother and, in particular, whether the injuries were sustained accidentally or by violent assault.

**Congenital malformations**

A maternal history of schizophrenia or affective disorder is a greater risk factor for perinatal death from congenital malformations than a maternal history of substance-related psychiatric disorders. The mechanism for this is unclear. One possible explanation might be the use of prescribed psychotropic drugs during pregnancy. Little research has been conducted in this field and our results require confirmation by replication using other datasets.

**CONCLUSION**

Future research is required to replicate our findings, particularly where we found high relative risks for small numbers of stillbirths or neonatal deaths in the exposed population. The raised risks related to psychiatric disorders are probably the result of a range of factors including social problems which can be hard to deal with. However, women who have contact with mental health services are a readily identifiable group for whom extra care during and after pregnancy may reduce preventable perinatal deaths. Our results indicate that obstetric, paediatric and mental health workers should be aware that women with mental health problems are in particular need of good reproductive health planning and antenatal care, ideally provided by multidisciplinary teams that can care for their complex range of physical and mental needs during pregnancy.

**Acknowledgements:** We thank Dr Louise Kenny for classifying the stillbirths and neonatal deaths in the exposed population. The raised risks related to psychiatric disorders are probably the result of a range of factors including social problems which can be hard to deal with. However, women who have contact with mental health services are a readily identifiable group for whom extra care during and after pregnancy may reduce preventable perinatal deaths. Our results indicate that obstetric, paediatric and mental health workers should be aware that women with mental health problems are in particular need of good reproductive health planning and antenatal care, ideally provided by multidisciplinary teams that can care for their complex range of physical and mental needs during pregnancy.

**REFERENCES**


APPENDIX

Table A1 shows the classification of causes of stillbirth and neonatal death.

Table A1  Classification of causes of stillbirth and neonatal death*

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Description and comments</th>
<th>ICD-10 1994-8†</th>
<th>ICD-8 1973–93†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stillbirths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal complications</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placental abruption and infarction</td>
<td>762.1–762.3, 762.9, 769.0, 769.1, 770.0–770.2</td>
<td>760.6–760.8</td>
</tr>
<tr>
<td></td>
<td>Poor growth of placenta</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interuterine growth restriction</td>
<td>770.8–771.1, 771.9, 776.1, 776.2, 777.0</td>
<td>772.1–772.5</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prematurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications of delivery</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anoxia</td>
<td>634.3, 764.4, 764.9, 765.0, 765.1, 765.4, 765.9</td>
<td>774.8–775.9</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>768.0, 768.3–768.5, 768.6, 768.9, 767.0, 767.4, 767.9</td>
<td>776.0–776.4</td>
</tr>
<tr>
<td></td>
<td>Prolapse of umbilical cord</td>
<td>769.9, 772.0, 772.8, 772.9, 776.0, 776.3, 776.4, 776.9</td>
<td>776.9</td>
</tr>
<tr>
<td></td>
<td>Difficult labour with various problems such as malposition of fetus and birth injury without mention of cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital malformations of the fetus</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spina bifida</td>
<td>740.0–749.9</td>
<td>759.0–759.9</td>
</tr>
<tr>
<td></td>
<td>Congenital anomalies of the heart, digestive system, urinary system, etc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal illness</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease of the mother</td>
<td>760.0–760.5, 761.1–761.3, 761.6, 761.7, 761.9</td>
<td>770.0–770.2</td>
</tr>
<tr>
<td></td>
<td>Chronic hypertension of the mother</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Maternal diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>An operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury to mother</td>
<td>Neither ICD-8 nor ICD-10 codes specify the type or cause of the injury to the mother which leads to the stillbirth</td>
<td>761.5</td>
<td></td>
</tr>
<tr>
<td>All other causes of stillbirth</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown causes of death</td>
<td>775.0, 775.9, 778.0, 778.2, 779.0, 779.9, 795.0, 170.6, 192.2, 199.1, 228.0, 320.9, 593.2, 778.0</td>
<td>778.1, 778.2, 778.9</td>
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<td></td>
<td>Cancers</td>
<td>772.0, 778.2, 778.9</td>
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<tr>
<td></td>
<td>Postmaturity</td>
<td>778.1, 778.2, 778.9</td>
<td></td>
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<td></td>
<td>Haemorrhages</td>
<td></td>
<td></td>
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<tr>
<td>Neonatal deaths</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incompetent cervix</td>
<td>769.0, 769.1, 767.1, 767.2, 777.0</td>
<td>769.0, 769.1</td>
</tr>
<tr>
<td></td>
<td>Premature rupture of membranes</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Respiratory distress of newborn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anoxia and birth injury to the brain</td>
<td>Includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficult labour with malposition of fetus with asphyxia, anoxia or hypoxia</td>
<td>764.5, 766.0, 766.4, 767.0, 767.4, 768.0, 772.0, 776.3, 776.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Birth asphyxia</td>
<td></td>
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</tbody>
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Continued
<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Description and comments</th>
<th>ICD-10 1994–9†</th>
<th>ICD-8 1973–93†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other conditions originating in the perinatal period</td>
<td>Includes: Other maternal conditions unrelated to pregnancy Conditions of placenta, placental infarction Conditions of umbilical cord Aspiration of contents of birth canal Cardiovascular disorders originating in the perinatal period</td>
<td>All other codes within P00.0–P99.9 not included in either immaturity or anoxia and birth injury to the brain</td>
<td>All other codes within 760.0–779.9 not included in either immaturity or anoxia and birth injury to the brain</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>Includes: Spina bifida Congenital anomalies of the heart, digestive system, urinary system, etc</td>
<td>Q00.0–Q99.9</td>
<td>740.0–759.9</td>
</tr>
<tr>
<td>All other causes of death (exposed population only)</td>
<td>Includes: Unknown causes of death and cancers</td>
<td>C76.7, D33.1, G71.1, X990</td>
<td>009.2, 038.9, 258.9, 273.9, 280.0, 285.9, 320.8, 320.9, 466.9, 486.0, 567.0, 795.0, 795.8, 796.2, 910.5, 913.9, 962.0</td>
</tr>
</tbody>
</table>

*These were the codes used for any maternal psychiatric illness. Owing to small numbers, we grouped together the maternal illnesses, injury to mother and all other causes of stillbirth categories for specific psychiatric diagnoses; †the codes are only those reported in the medical births or cause-of-death registers as the primary cause of stillbirth or death in Denmark 1973–98; ‡the codes in the unexposed population are too numerous to be included in this table. They may be obtained from the corresponding author.