Recurrence of Gestational Age in Sibships: Implications for Perinatal Mortality

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The authors studied the extent to which preterm birth and perinatal mortality are dependent on the gestational ages of previous births within sibships. The study was based on data collected by the Medical Birth Registry of Norway from 1967 to 1995. Newborns were linked to their mothers through Norway's unique personal identification number, yielding 429,554 pairs of mothers and first and second singleton newborns with gestational ages of 22-46 weeks, based on menstrual dates. Siblings' gestational ages were significantly correlated (r = 0.26). The risk of having a preterm second birth was nearly 10 times higher among mothers whose firstborn child had been delivered before 32 weeks' gestation than among mothers whose first child had been born at 40 weeks. However, perinatal mortality in preterm second births was significantly higher among mothers whose first infant had been born at term, compared with mothers whose firstborn child was delivered at 32-37 weeks. Since perinatal mortality among preterm infants is dependent on the gestational age in the mother's previous birth, a common threshold of 37 weeks' gestation for defining preterm birth as a risk factor for perinatal death may not be appropriate for all births to all mothers. Am J Epidemiol 1999;150:756-62.

Women who deliver a low birth weight baby in their first pregnancy have an increased risk of delivering a low birth weight baby in their next pregnancy (1-3), and studies have shown that this dependence between siblings has implications for perinatal mortality rates (3-8). A low birth weight baby (<2,500 g) has a lower risk of dying during the perinatal period if its preceding sibling was small at birth than if the preceding sibling was normal weight at birth (3).

Recurrence of preterm delivery has also been found (1, 7-13), but hardly any studies have focused on whether this has implications for perinatal mortality among siblings (13). In addition, studies focusing on gestational age generally use broad categories ("full term" vs. "preterm" birth), and details within these categories have been less focused.

In the present study, we characterized the gestational age relation within sibships by examining the gestational age of second births according to the gestational age of first births. We also considered whether the sibling link in gestational age has implications for perinatal mortality.

MATERIALS AND METHODS

Since 1967, information on all births occurring in Norway, including stillbirths of ≥16 weeks' gestation, has been compiled by the Medical Birth Registry of Norway. Soon after birth, the Norwegian Central Bureau of Statistics gives all liveborn infants a unique personal identification number. These numbers are systematically linked to the birth records by means of the mother's personal identification number. The registry records are routinely linked to the files on infant death obtained from the Central Bureau of Statistics.

Through the personal identification number, successive births to each woman in this study were linked, providing us with 489,778 mothers who had had at least two singleton births during the period 1967-1995, and whose first births occurred in 1967 or later. Only information on the two first births to each woman was included in the study.

Our definitions of preterm, full term, and postterm birth followed the standard definitions recommended by the World Health Organization (14). We excluded 1,774 pairs of births (0.4 percent) in which the first
sibling, the second sibling, or both siblings had a registered gestational age below 22 weeks, as well as 4,313 pairs (0.9 percent) with a registered gestational age above 46 weeks. We also excluded 50,653 pairs of births (10.3 percent) for which information on gestational age was missing for either delivery. This left us with a population of 433,038 sibling pairs. Some details about the infants with missing gestational age as compared with infants included in the final study population are given in table 1.

Gestational age was based on the reported date of the last menstrual period. This approach has certain limitations, as do other methods of assessing the duration of pregnancy (15, 16). The Medical Birth Registry gives the reported date of the last menstrual period without any further details, and a proportion of the menstrual dates will be uncertain. In order to exclude obviously misclassified births in the preterm period, we assumed the birth weight distribution at each completed week of gestation to be predominantly Gaussian (17-19). Many of the misclassified births show up as residual births in the right tail of the distribution (heavy births). Parameters of the predominant Gaussian distribution were estimated on the basis of the left part of the distribution using specially developed Fortran computer programs (3). The births falling outside of the right tail of the predominant distribution (misclassified births) were excluded from the population. The births falling into the area with overlap between the predominant distribution and the right-tail residual distribution were weighted 0 (to be excluded) or 1 (to be included) according to their probability of belonging to the predominant distribution. A total of 3,484 mothers (0.8 percent) with a presumed misclassified birth were thus excluded, and the final study population left for analysis comprised 429,554 sibling pairs. We also performed the analyses with the misclassified births included.

Perinatal mortality was calculated as stillbirths occurring from the 22nd week of gestation onward, plus early neonatal deaths occurring within the first 7 days of life, per 1,000 births.


Interpregnancy interval was computed as the amount of time between the birth of the first child and the conception of the second child. It was categorized into quartiles.

The following possible confounding variables were evaluated: mother’s age at the first birth (grouped into three categories: ≤19 years, 20–34 years, and ≥35 years), mother’s marital status at the second birth (in two categories: single and married/cohabiting), time period (five categories), and interpregnancy interval (four categories).

Data handling and statistical analyses were carried out using SPSS software (20). The confidence intervals for the correlation coefficient were calculated using Fisher’s $z$ transformation. Odds ratios were calculated from contingency tables or by logistic regression. Logistic regression analyses were used to evaluate confounding and to test for trends (20).

**RESULTS**

**Gestational age correlations and recurrence of preterm birth**

The mean gestational age for first births was 39.85 weeks (standard deviation (SD) 2.23), and for second births it was 39.84 weeks (SD 2.00). The percentage of preterm births among first and second births was 5.34 percent and 3.94 percent, respectively ($p$ for difference < 0.0001).

Table 2 shows mean gestational age, percentage of preterm births, and perinatal mortality (total and preterm) in the population of second births for the following gestational age categories of first births: extremely preterm (22–27 weeks), very preterm (28–31 weeks), moderately preterm (32–34 weeks),
TABLE 2. Characteristics of 429,554 second births, according to the gestational age category of first births, Norway, 1967–1995

<table>
<thead>
<tr>
<th>Gestational age in the first birth (completed weeks)</th>
<th>No.</th>
<th>%</th>
<th>Mean gestational age (weeks)</th>
<th>Standard deviation</th>
<th>% preterm (born before 37 weeks’ gestation)</th>
<th>Perinatal mortality rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>22–27</td>
<td>1,869</td>
<td>0.4</td>
<td>37.6</td>
<td>4.3</td>
<td>24.4</td>
<td>73.8</td>
</tr>
<tr>
<td>28–31</td>
<td>2,490</td>
<td>0.6</td>
<td>37.9</td>
<td>3.6</td>
<td>22.9</td>
<td>49.0</td>
</tr>
<tr>
<td>32–34</td>
<td>5,624</td>
<td>1.3</td>
<td>38.4</td>
<td>2.8</td>
<td>17.4</td>
<td>24.5</td>
</tr>
<tr>
<td>35–36</td>
<td>12,934</td>
<td>3.0</td>
<td>38.8</td>
<td>2.5</td>
<td>12.3</td>
<td>16.6</td>
</tr>
<tr>
<td>37</td>
<td>15,256</td>
<td>3.6</td>
<td>39.0</td>
<td>2.3</td>
<td>8.3</td>
<td>13.0</td>
</tr>
<tr>
<td>38</td>
<td>33,644</td>
<td>7.8</td>
<td>39.2</td>
<td>2.0</td>
<td>5.7</td>
<td>9.7</td>
</tr>
<tr>
<td>39</td>
<td>75,388</td>
<td>17.6</td>
<td>39.5</td>
<td>1.9</td>
<td>3.9</td>
<td>9.0</td>
</tr>
<tr>
<td>40</td>
<td>114,358</td>
<td>26.6</td>
<td>39.9</td>
<td>1.8</td>
<td>3.0</td>
<td>8.7</td>
</tr>
<tr>
<td>41</td>
<td>96,534</td>
<td>22.5</td>
<td>40.2</td>
<td>1.8</td>
<td>2.3</td>
<td>8.0</td>
</tr>
<tr>
<td>42–46</td>
<td>71,457</td>
<td>16.6</td>
<td>40.5</td>
<td>1.9</td>
<td>2.2</td>
<td>8.4</td>
</tr>
</tbody>
</table>

* No. of deaths per 1,000 births.

mildly preterm (35–36 weeks), full term (37, 38, 39, 40, and 41 weeks), and postterm (42–46 weeks). The mean gestational age of second births increased by increasing gestational age of first births. The highest percentage of preterm second births was found in sibships with extremely preterm first births, and the percentage decreased successively by increasing gestational age of first births.

We found a clear correlation between the gestational ages of the first and second births to each mother (Pearson’s $r = 0.260$; 95 percent confidence interval (CI): 0.257, 0.263). This correlation is illustrated in figure 1.

The overall relative risk of delivering a second child preterm after a first child had been born preterm, compared with mothers whose firstborn was delivered full term, was 4.8 (95 percent CI: 4.6, 5.0); the odds ratio was 5.5 (95 percent CI: 5.3, 5.7). Adjustment for the possible confounding variables of mother’s age, mother’s marital status, time period, and interpregnancy interval only slightly reduced the estimated odds ratio (adjusted odds ratio = 5.3; 95 percent CI: 5.1, 5.5).

A mother’s absolute risk of delivering a second child preterm was related to the exact gestational age of her firstborn child. For mothers who had delivered their first infant before 32 weeks’ gestation, the risk was found to be above 20 percent. After this there was a nearly linear decrease in risk, such that for mothers delivering their first child at 40 weeks, the absolute risk of delivering a second child preterm was 3.0 percent (95 percent CI: 2.9, 3.1) (figure 2).

Implications for perinatal mortality

There was a clear reduction in the perinatal mortality rate for the total population of second births as the gestational age of first births increased and the proportion of preterm second births decreased, supporting the well recognized association between perinatal mortality and preterm delivery (table 2). However,
perinatal mortality for the preterm second births was at its lowest level when the first birth itself had been mildly preterm (table 2). Furthermore, within the preterm categories of second births, the perinatal mortality rate increased successively as the gestational age of the first birth increased from 32 weeks’ gestation (figure 3). This increase in mortality was assessed by logistic regression for each category of preterm second birth, and with first births’ gestational ages restricted to the range of 32–41 weeks. The increase in mortality was found to be statistically significant for the second births in the very preterm (28–31 weeks; $p = 0.05$), moderately preterm (32–34 weeks; $p < 0.0001$), and mildly preterm (35–36 weeks, $p < 0.0001$) categories, whereas for the extremely preterm second births (22–27 weeks) there was no significant increase.

**Time trends**

Pregnancy duration for first and second siblings was stable during the nearly 30-year time span of this study, and there was also a fairly stable incidence of preterm birth. However, the odds ratio for a preterm second birth among mothers with a previous preterm birth as compared with mothers with a previous full term birth increased slightly over the study period, from 4.9 in 1967–1971 to 5.3 in 1972–1976, 5.6 in 1977–1981, 5.9 in 1982–1986, and 6.1 in 1987–1991 (test for trend: $p < 0.0001$). To adjust for possible confounding by maternal age, marital status, interpregnancy interval, and time period, we assessed these time trends using logistic regression. We found a statistically significant interaction between time period and previous preterm birth (Wald test, $p = 0.004$). The corresponding adjusted odds ratios were 4.8, 5.0, 5.4, 5.8, and 6.0. The absolute risk of having a preterm second birth for mothers with a preterm first birth increased from 15.7 percent during the first period to 16.3 percent during the last period, while the corresponding risks were 3.7 percent and 3.1 percent among mothers whose first infant had been delivered at term.
DISCUSSION

We found that mothers with a preterm delivery in their first pregnancy had an increased relative risk for preterm delivery in their next pregnancy. Mothers with preterm second births experienced lower perinatal mortality when their firstborn child was delivered mildly preterm as compared with full term.

Gestational age in our study was based on menstrual dates. These figures include uncertainty about the date of the last menstrual period (i.e., forgotten dates, prolonged amenorrhea, oral contraceptive use, cyclical bleeding after conception, and biologic variation in the menstrual cycle). Our register-based study contained no information on the accuracy of the reported menstrual dates, and thus some births may have been misclassified. If these errors were correlated in pregnancies occurring in the same mother—for instance, among women who bleed early in pregnancy (21)—they could possibly have contributed to the pattern we observed in our data. However, for the misclassifications to have influenced the correlation pattern substantially, there would have to have been a considerable quantity of large misclassifications, and there also must have been an extremely high risk of repeating such misclassifications in the following pregnancies.

There is no easy solution to the problem of erroneous gestational age measurements. The two most commonly used approaches are correcting uncertain menstrual dates by ultrasound estimates (22, 23) and examining the distribution of birth weights within gestational age strata (17, 24, 25). Ultrasound assessment based on fetal size in early pregnancy has been chosen by many as the “gold standard,” but these estimates are also subject to error (15, 16, 23). There is a natural variation in fetal size at the time of measurement. Since the date of the last menstrual period is the basis for the timing of the first ultrasound measurement, the ultrasound estimate is not independent of gestational age.

We have attempted to exclude misclassified preterm births by analyzing the distribution of birth weights for each completed week of gestation (17–19). The method is based on an assumption of Gaussian distributions and suffers from the problem of overlapping distributions. However, since the Gaussian distribution has light tails, we believe that the most extremely misclassified values were excluded. The exact numbers of incorrectly included births in our study are unknown to us and could have influenced the results. Nevertheless, when misclassified births are excluded by our method, the results actually get stronger, indicating that misclassifications dilute the results rather than enhance them.

We confirm that gestational age is correlated in sibships (1, 7, 11). We also confirm that mothers with a preterm delivery in their first pregnancy have an increased relative risk of preterm delivery in their next pregnancy (1, 10, 13), although they will have the greatest absolute chance of delivering at term, regardless of the length of the preceding pregnancy. However, we do find that the absolute risk of delivering a second child preterm is related to the exact gestational age of the firstborn child. In addition, there are different relations for sibships with firstborns delivered before 32 weeks and those with firstborns delivered after 32 weeks, suggesting heterogeneity in the factors that are important for sibling-associated pregnancy duration. Pathologic factors that distort the normal regulators of pregnancy duration may be more common among pregnancies that end before 32 weeks, and such factors may contribute to the deviating relations in sibships including very preterm infants as compared with sibships including mildly and moderately preterm infants.

The present study suggests that siblings may share some underlying factors involved in the initiation of labor. Both genetic (fetal and maternal) and environmental factors may be involved. The uterine environment in which the fetus develops is a function of compound determinants like the mother's genotype, her reproductive history, and her own gestational experience (26–28), as well as external environmental factors such as lifestyle habits and exposure to toxins. In the present study, we did not have enough data to distinguish between the likely etiologies of any particular recurrence of preterm delivery, and this may constitute a problem when interpreting crude patterns of recurrence.

If fetal genes play a major role in the variation of pregnancy duration, one would expect to see intergenerational effects—i.e., a positive correlation between the lengths of gestation of the parents and the offspring. This was studied by Magnus et al. (29) in the same study population as ours; the correlation between the gestational ages of mothers and offspring was found to be low (r = 0.09), but the correlation was higher for birth weight (r = 0.24). It has been suggested that human variation in gestational age is not influenced by genetic factors to the same degree as birth weight. However, a recent study by Klebanoff et al. (30) showed a slightly increased risk of preterm birth among mothers who themselves had been born preterm, and one still cannot totally exclude genetic factors as contributors to the variation of pregnancy duration.

In this study, gestational age had a strong impact on perinatal mortality. However, within preterm categories of second births, perinatal mortality rates were higher the later the older siblings were delivered. Mothers delivering a second baby preterm experienced
partly explained as a result of more specialized care in births in sibships with a preterm first birth may be. Rates per se, would be interesting.

The perinatal period, in addition to perinatal mortality focusing on deaths due to conditions that originate in effective prenatal and neonatal care. Further studies will thus be concealed if we do not take into account the exact gestational age of the older sibling. The standard definition of preterm birth as a risk factor for perinatal death, with a common threshold of 37 weeks' gestation for all births to all mothers, based on cross-sectional data, may thus seem inappropriate in a clinical context where prediction of risk is important.

Skjærven et al. (3) found similar effects on perinatal mortality by birth weight categories in first births, and concluded that an individual baby's risk of perinatal death is largely a function of its birth weight relative to the usual weight of infants born to that mother. They recently demonstrated a similar relation between maternal birth weight and offspring birth weight (31). As for birth weight, it may be that some women are more prone to giving birth after shorter pregnancies than other women, and that the mortality risk associated with being born "early" is lower for these mothers' babies. Even though the biologic interpretation of this hypothesis is not evident on the basis of our data, the finding is relevant, especially for antenatal care, and further studies should be initiated.

We examined perinatal mortality in our study. It is relevant to discuss whether stillbirths should be excluded from a study in which one of the aims is to predict mortality. However, we repeated our analyses using neonatal mortality (death during the first month) as the outcome, and the main trends in our results were still present. Since perinatal mortality is a commonly used outcome and numbers are larger when we include stillbirths, we have chosen to report variations in perinatal mortality. However, one should consider that the meaning of perinatal mortality might have changed during the long observation period of our study. Deaths that previously occurred in utero and during the first week of life may have been postponed to older ages during more recent periods, because of more effective prenatal and neonatal care. Further studies focusing on deaths due to conditions that originate in the perinatal period, in addition to perinatal mortality rates per se, would be interesting.

The lower risk of perinatal death for preterm second births in sibships with a preterm first birth may be partly explained as a result of more specialized care in second pregnancies: If a mother has delivered a first child preterm, health care professionals will view her next pregnancy as high risk, and may refer her to specialized care or be particularly alert when following her; this would result in a lower perinatal mortality rate for preterm second births. However, we found the same relations as those described in our results when comparing perinatal mortality risks for second preterm births in all regions of Norway, some with many specialists and short distances to hospitals and others with fewer specialists and longer distances.

During the time span of our study, the relative risk of repeating a preterm delivery increased. This indicates success during the past 30 years in preventing a number of the preterm births that should not occur (those in mothers who are supposed to have longer pregnancies), and relatively more of the preterm second births at the end of the study period occurred among mothers who were biologically "set" to have shorter pregnancies.

We conclude that the risk of delivering a preterm second baby is related to the exact gestational age of the first baby. Infants of mothers who repeat a preterm birth have lower perinatal mortality than those of mothers who deliver a second child preterm after a first child has been born full term.

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