Risk factors and prognostic models for preterm birth
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Recurrence risk of preterm birth in subsequent twin pregnancy after preterm singleton delivery

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Abstract

Objective  In women with a multiparous singleton pregnancy, previous preterm birth is the most important risk factor for subsequent preterm birth. Little is known whether this recurrence risk also holds if the next pregnancy is a twin gestation. We aim to determine the risk of preterm birth in a subsequent twin pregnancy after previous singleton preterm birth.

Design  Cohort study

Setting  Nationwide study in the Netherlands

Population  We studied 4071 nulliparous women who had a singleton delivery followed by a subsequent twin delivery between the years 1999 and 2007.

Methods  We compared outcome of subsequent twin pregnancy of women with a history of preterm singleton delivery to pregnancy outcome of women with a history of term singleton delivery. We subdivided first delivery in iatrogenic and spontaneous preterm deliveries. Furthermore we performed analyses by subgroups for gestational age at the time of singleton delivery.

Main outcome measure  Spontaneous preterm birth (<37 weeks) in subsequent twin pregnancy.

Results  In the index singleton pregnancy, preterm birth occurred in 232 (5.7%) of 4071 women. The risk of subsequent twin preterm birth was significantly higher after previous singleton preterm delivery (56.9% versus 20.9%; odds ratio 5.0; 95% CI 3.8-6.6). Risk of subsequent twin preterm birth was dependent on the severity of previous singleton preterm birth and was highest after preceding spontaneous instead of iatrogenic singleton preterm delivery.

Conclusion  Preterm birth of a singleton gestation is associated with an increased risk of spontaneous preterm birth in a subsequent twin pregnancy.
Preterm birth, defined as birth before 37 completed weeks of gestation, is one of the major concerns in modern obstetric healthcare. It is the most common cause of perinatal morbidity and mortality in developed countries.\(^1\,^2\) This is often due to respiratory immaturity, intracranial haemorrhages and infections.\(^3\) Preterm birth can occur spontaneously or can be a result of medical intervention in the case of severe pregnancy complications like pre-eclampsia or intra uterine growth restriction.\(^4\) The incidence of preterm birth has been steadily rising in most developed countries during the last decades, mainly caused by an increase in iatrogenic preterm births.\(^5\,^7\) Risk of preterm birth varies between 5-15% in developed countries. Preterm birth is associated with an increased risk of preterm birth in the subsequent pregnancy. In fact, a history of previous preterm birth is, together with multiple gestation, the most important risk factor in the aetiology of preterm birth. This increased risk is well established and reconfirmed in several studies reporting odds ratios of approximately 3 for the recurrence of preterm birth.\(^5\,^9\) However, these studies only focused on the risk of singleton preterm birth after a previous singleton birth. Little is known whether the recurrence risk also holds for twin pregnancies following a preceding singleton preterm birth. To our knowledge, only four studies reported on this subject using different methodological approaches.\(^10\,^13\) Therefore, we aim to further investigate the recurrence risk of preterm birth in subsequent twin pregnancy following previous preterm singleton delivery.

**Materials and Methods**

**Dataset**

This study was performed in a nationwide prospective cohort using the Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns.\(^14\,^15\) The coverage of the PRN registry is about 96% of all deliveries in The Netherlands. It contains pregnancies ≥ 22 weeks and a birthweight ≥ 500 grams. The records included in the PRN are entered at the child’s level.

**Longitudinal linkage**

There is no unique maternal identifier available in the registry to follow-up on outcomes of subsequent pregnancies of the same mother. Therefore, we performed a probabilistic linkage procedure in which we longitudinally linked records of children of the same mother in order to create a mother identifier.
We subjected all children from second deliveries (n=509,559) registered in the PRN registry to linkage with their siblings born during a first delivery (nulliparous woman) registered in the PRN registry. The longitudinal linkage was based on the variables birth date of mother, birth date of (previous) child, and postal code of mother and is further described in the Appendix (see Chapter 5). The final linked cohort with complete data on first and second deliveries of the same mother consisted of 272,551 women and 545,102 (2 x 272,551) deliveries.

Inclusion and exclusion criteria
From our linked cohort we included all multiparous women who delivered a twin pregnancy (second delivery) after a previous singleton pregnancy (first delivery) in the Netherlands between January 1\textsuperscript{st} 1999 and December 31\textsuperscript{st} 2007. We excluded all cases with antepartum fetal mortality and all cases with major congenital anomalies. Furthermore we excluded iatrogenic preterm births in the subsequent twin pregnancies as we were only interested in the subsequent risk of spontaneous preterm birth. Preterm birth was defined as birth before 37 completed weeks of gestation.

Statistics
We compared baseline characteristics of women with a preterm singleton delivery to those with a term singleton delivery. For these two groups we compared demographic and obstetric baseline characteristics like maternal age (mean ± SD), socio economic status (low (<p25) versus >p25), white maternal ethnicity (yes versus no), living in a deprived area (yes versus no) use of ART (yes versus no), and pregnancy interval (mean ± SD).

We subdivided nulliparous singleton preterm deliveries in spontaneous and iatrogenic deliveries. We also subdivided previous preterm birth into three subgroups (22\textsuperscript{0}-29\textsuperscript{6} weeks, 30\textsuperscript{0}-33\textsuperscript{6} weeks and 34\textsuperscript{0}-36\textsuperscript{6} weeks). Univariate analyses of the baseline characteristics were performed with the Student $t$ test for normally distributed continuous variables and chi-square test for categorical variables. Normality of continuous variables was assessed by visual inspection of Q-Q plots. All statistical tests were 2-sided and a p-value of 0.05 was chosen as the threshold for statistical significance. We measured the association between history of preterm birth and subsequent risk of spontaneous preterm birth by calculating an adjusted odds ratio (aOR). We only adjusted for variables that appeared to be differently distributed in the baseline characteristics of the study population.

The probabilistic linkage procedure was performed using the R statistical software environment version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and the data were analyzed using SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA).
Results

After the longitudinal linkage procedure (see Appendix Chapter 5) we were able to identify 5307 mothers who had a twin delivery following a previous index singleton delivery. After excluding mothers with iatrogenic preterm births in the second pregnancy (21%), severe congenital anomalies in first or second pregnancy (1.0% and 1.2% respectively), and antepartum fetal mortality (1.1% and 0.5% respectively) we had 4071 women with complete follow-up data.

Baseline characteristics of this cohort are presented in table 1. In the singleton pregnancy 232 (5.7%) women delivered before 37 completed weeks of gestation. In the majority of cases these preterm births occurred spontaneously (n=147; 63%), but were a result of obstetrical intervention in the remaining 85 (37%) women. Demographic characteristics of the women with preterm (n=232) and term (n=3839) singleton deliveries were comparable when considering maternal age, maternal ethnicity, socio economic status, living in a deprived area, and pregnancy interval. Nonetheless, there were significantly more women who used artificial reproductive technology in the group with preterm singleton deliveries (35.3% versus 27.9%, p<0.05).

Figure 1 visualises the relation between gestational age in the nulliparous singleton delivery and subsequent twin delivery. Of the 232 women who had a preterm singleton delivery, 132 women (56.9%) had a spontaneous preterm birth in the subsequent twin pregnancy and 100 (43.1%) women delivered at term. The spontaneous twin preterm birth rate in the 3839 women who delivered their singleton at term was 20.9% (n=804). Delivery of preterm singleton was thus associated with a significant increased risk of spontaneous preterm birth in a subsequent twin pregnancy (aOR 5.0; 95% CI 3.8-6.6).

Figure 1. Distributions of gestational age (in weeks) in nulliparous singleton delivery and subsequent twin delivery. To illustrate the relation between the two gestational ages, we predicted the gestational age at the second delivery using the gestational age of the first delivery. The estimated mean (continuous line) and its corresponding 95% confidence interval (dotted line) are presented.
Table 1. Baseline maternal characteristics of the cohort (n=4071) stratified by gestational age at the singleton delivery

<table>
<thead>
<tr>
<th>Characteristics of the singleton delivery</th>
<th>Preterm singleton delivery</th>
<th>Term singleton delivery</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;37 weeks (n=232)</td>
<td>≥37 weeks (n=3839)</td>
<td></td>
</tr>
<tr>
<td>Mean maternal age at twin delivery in years (±SD)</td>
<td>29.8 ± 3.8</td>
<td>29.4 ± 4.0</td>
<td>0.19</td>
</tr>
<tr>
<td>White maternal ethnicity (n)</td>
<td>219 (94.4%)</td>
<td>3526 (91.9%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Low socio-economic status (n)</td>
<td>36 (15.5%)</td>
<td>775 (20.2%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Living in a deprived area (n)</td>
<td>5 (2.2%)</td>
<td>154 (4.0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Artificial reproductive technology (n)</td>
<td>82 (35.3%)</td>
<td>1072 (27.9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median interval to subsequent twin pregnancy in months (IQR)</td>
<td>28 (21-39)</td>
<td>28 (22-37)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows the subdivision in spontaneous versus iatrogenic preterm singleton delivery. It shows that the increased risk of subsequent twin preterm birth is highest after a spontaneous preterm singleton delivery (aOR 7.8; 95% CI 5.5-11.2) instead of an iatrogenic preterm singleton delivery. Nevertheless, even after an iatrogenic preterm singleton delivery there is still an increased risk of spontaneous preterm birth in the next twin pregnancy (aOR 2.4; 95% CI 1.5-3.8). Table 2 shows that for iatrogenic preterm singleton deliveries the recurrence risk also depends on the gestational age at the time of preterm singleton delivery. The risk of preterm birth increases as the gestational age at preterm singleton delivery decreases. The odds ratios in table 2 are adjusted for artificial reproductive technology and socio-economic status.

Table 2. Risk of spontaneous preterm birth of twin pregnancy in women with a history of singleton delivery (n=4071) Stratification by subtype of preterm birth and gestational age at time of previous singleton delivery

<table>
<thead>
<tr>
<th>Gestational age at delivery (weeks)</th>
<th>Number</th>
<th>Spontaneous preterm birth</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall term delivery ≥ 37 weeks</td>
<td>3839</td>
<td>804</td>
<td>20.9%</td>
</tr>
<tr>
<td>Overall preterm delivery &lt; 37 weeks</td>
<td>232</td>
<td>132</td>
<td>56.9%</td>
</tr>
<tr>
<td>Spontaneous preterm delivery &lt; 37 weeks</td>
<td>147</td>
<td>99</td>
<td>67.3%</td>
</tr>
<tr>
<td>34²⁺⁶⁻³⁶⁶⁺weeks</td>
<td>126</td>
<td>83</td>
<td>65.9%</td>
</tr>
<tr>
<td>30²⁺³⁻³³⁶⁺weeks</td>
<td>14</td>
<td>11</td>
<td>78.6%</td>
</tr>
<tr>
<td>22²⁺⁶⁻²⁹⁶⁺weeks</td>
<td>7</td>
<td>5</td>
<td>71.4%</td>
</tr>
<tr>
<td>Iatrogenic preterm delivery &lt; 37 weeks</td>
<td>85</td>
<td>33</td>
<td>38.8%</td>
</tr>
<tr>
<td>34²⁺⁶⁻³⁶⁶⁺weeks</td>
<td>64</td>
<td>22</td>
<td>34.4%</td>
</tr>
<tr>
<td>30²⁺³⁻³³⁶⁺weeks</td>
<td>12</td>
<td>6</td>
<td>50.0%</td>
</tr>
<tr>
<td>22²⁺⁶⁻²⁹⁶⁺weeks</td>
<td>9</td>
<td>5</td>
<td>55.6%</td>
</tr>
</tbody>
</table>

* Adjusted for: artificial reproductive technology and socio-economic status
Principal findings
We investigated the risk of spontaneous preterm twin birth in women with a history of singleton delivery. We found that the risk of subsequent twin preterm birth is significantly increased after a previous preterm singleton delivery when compared to a previous term singleton delivery.

Strengths and weaknesses
Our study was based on data of a large population-based national perinatal registry. The majority of the caregivers contribute to the PRN registry and it thus comprises approximately 96% of all pregnancy and birth characteristics in the Netherlands. The 4% missing birth data are due to 1-2% non-reporting general practitioners and 2-3% non-reporting midwives. As (threatened) preterm delivery and multiple gestation are an indication for referral to an obstetrician and the registration by obstetricians is nearly complete (>99%), we would not have missed many cases due to non-reporting.

For our analyses we performed a probabilistic linkage method to follow-up mothers in a subsequent pregnancy. Of the 509,559 second deliveries in the PRN registry we were able to find the matching first delivery in 272,551 (53%) cases. Non-linkage could be due to missing values of the linkage variables, but is mainly due to the fact that the first child was born before the start of the PRN registry in 1999. The latter argument accounts for approximately half of the non-linked deliveries. Furthermore, the small number of available linkage variables also influenced the linkage rate. Finally, as postal code of mother is one of the linkage variables, changes of home address over time will also have led to non-linkage. We found that our linked dataset of 272,551 women are comparable to the national figures for demographic characteristics (e.g. maternal age) and pregnancy outcomes (e.g. congenital abnormalities, pregnancy length and preterm birth rates). Only the twin pregnancy rate and the perinatal mortality rate in the linked dataset seem to be different from the original dataset. This only holds for the incidence rates in the first pregnancy (appendix S1). However, we do not think that non-linked pregnancies have influenced our results to a large degree as non-linkage is not related to gestational age at nulliparous singleton delivery, nor to the primary outcome measure.

Relation to other studies
To the best of our knowledge, four previous studies on this topic were published presenting conflicting results and conclusions. The most recent study was performed by Facco et al. where they investigated 193 women in a 10-year hospital-based retrospective cohort. The risk of spontaneous preterm twin birth was 73.9% after previous spontaneous singleton preterm birth and 44.4% after previous term singleton delivery (odds ratio 3.5; 95% CI 1.4-9.3). These results are in accordance with our findings. Another study performed by Ananth et al. also concluded that women with a history of singleton preterm birth carry an increased risk of preterm birth in the subsequent twin pregnancy.
This population-based retrospective study included 2329 women in the state of Missouri between 1989 and 1997. The risk of spontaneous preterm twin birth was 43.6% after previous spontaneous singleton preterm birth and 31.2% after previous term singleton delivery. They also found that the risk of subsequent preterm birth increased based on the severity of the previous preterm birth. Bloom et al. found that of the 179 women with a preterm (<35 weeks) twin deliveries included in their study, 16% had a history of prior preterm birth compared to 5% of those who delivered beyond 35 weeks. Unfortunately, the investigators did not describe any baseline characteristics, nor did they specify whether the prior preterm birth had a spontaneous or iatrogenic onset of labour. Finally, our findings show similarities with those presented by Rydhstroem.\textsuperscript{13} The author also analyzed previous preterm births as a whole, instead of subdividing them into iatrogenic and spontaneous preterm births.

Meaning of the results and future research
The evidence of the recurrence risk of preterm birth after a previous singleton preterm birth is consistent and substantial.\textsuperscript{8,9} We have now demonstrated a similar increased recurrence risk for a twin pregnancy following preterm singleton delivery. This increased risk is found after spontaneous as well as iatrogenic preterm delivery. The latter might be explained by the presence of risk factors that both contributed to the need of medical intervention in the first singleton pregnancy, as well as to the pathogenesis of spontaneous preterm birth in the next twin pregnancy. To the best of our knowledge our study has the largest sample size in the investigation of twin preterm birth after preceding singleton delivery.

Twin pregnancy is one of the most important risk factors for preterm birth. The pathogenesis of preterm birth in twins remains largely unknown, but is claimed to be partly caused by excessive myometrial stretch.\textsuperscript{16} However, our findings implicate that other mechanisms must also exist as the risk of preterm twin birth is even further increased in the case of previous singleton preterm birth. This merits further research on other underlying risk factors that cause preterm birth in twin pregnancies. Our study can also have implications for patient counselling and can help obstetric caregivers better quantify the risk of preterm delivery.

Conclusion
Women with a history of singleton preterm birth are at increased risk for spontaneous preterm birth in a subsequent twin pregnancy.


