Is the risk of still and preterm birth affected by the timing of symptomatic SARS-CoV-2 infection during pregnancy? – Data from the CRONOS Network, Germany

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Research Letter: 498
Number of References: 4
Number of Tables/Figures: 1

Condensation:
The risk for preterm birth and stillbirth after symptomatic Sars-CoV-2 in pregnancy is increased especially after early infection and within the first 4 weeks after infection.

Short title
Preterm Birth Risk after symptomatic Sars-CoV-2 in pregnancy
**AJOG at glance**

*Why was this study conducted?*

This study aimed to elucidate the associations between the timing of symptomatic SARS-CoV-2 infection during pregnancy and the risk of still and preterm birth.

*Key findings:*

In this prospective observational study including 1149 symptomatic SARS-CoV-2 infected pregnant women, infection within the first two trimesters of pregnancy was associated with an increased risk of early preterm birth (PTB) (≤32 weeks) and stillbirth compared to infection within the third trimester. The risk of PTB was higher within the first 4 weeks after infection.

*What does this add to what is known?*

Infection should be prevented during pregnancy. Pregnant women with a SARS-CoV-2 infection during the early pregnancy could benefit from extensive obstetric surveillance during the rest of gestation.

*Key Words:*

Preterm Birth, Stillbirth, Sars-CoV-2 Infection in Pregnancy, Obstetric Surveillance, Vaccination in Pregnancy

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**Research Letter:**

**Background:** SARS-CoV-2 infection during pregnancy results in higher risk of preterm births (PTB). Recently, it has been shown that the gestational age at infection but not the severity of the infection has a significant impact on PTB rate.

**Objective:** The aim of this study is to analyze the association of timing of symptomatic SARS-CoV-2 infection during pregnancy with PTB- and stillbirth-risk.

**Study Design:** From 04/03/2020 to 08/24/2021 data of 2650 women with confirmed SARS-CoV-2 infection during pregnancy from 113 hospitals in Germany and Austria (covering about 30% of all deliveries in Germany) were collected in the prospective register “COVID-19 Related Obstetrics and Neonatal Outcome Study” (CRONOS). Exclusion criteria were defined as: (1) asymptomatic infection, (2) SARS-CoV-2 infection after 37+0 weeks of gestation (wks), (3) miscarriage before 20+0 wks and (4) incomplete data in regard of infection/delivery date, live birth, maternal age, admission due to SARS-CoV-2 symptoms/obstetrics reasons or history of stillbirth/PTB in prior pregnancies. Timing of exposure was dichotomized into early
(first/second trimester) and late (third trimester) infections. The primary endpoints were PTB (classified into early PTB \( \leq 32 \) and late PTB >32 wks) and stillbirth. Association was assessed using log-binominal regression models for calculating adjusted relative risk (aRR) and 95% confidence intervals (95%-CI). Secondary endpoints were defined as delivery within 4 weeks after SARS-CoV-2 infection, occurrence of other pregnancy complications. For categorical variables, Chi-Square or the Fisher exact test (n<5) were used. All statistical analyses were performed using SPSS Version 27 for Windows (IBM Corp.).

Results: A total of 1149 patients were eligible for the final analysis: 1128 (98.2%) gave a live birth, of those 201 (17.8%) were preterm (supplements figure 1). 21 (1.8%) stillbirths occurred (supplements table 1). More than half of the analyzed women acquired the infection in third trimester, 45.5% earlier in pregnancy. Of the 1084 women with known immunization status, no one was vaccinated at time of infection.

Early symptomatic SARS-CoV-2 infection increased the risk of early PTB (aRR=2.07; 95%-CI 1.10–3.91) and stillbirth (aRR=2.76; 95%-CI 1.15–6.64) compared to a late infection (table 1). The risk of PTB was higher within 4 weeks after infection (RR=4.89; 95% CI 3.86-6.19). Threatened preterm birth (RR= 1.80; 95% CI 1.07 – 3.01) and gestational cholestasis (RR= 3.18; 95% CI 1.19 – 8.44) occurred more often in late infections.

Conclusion: 17.8% of the symptomatic infected women delivered preterm – more than double compared to the general German preterm birth rate of nearly 9 % \(^3\). Hospitalization for any reason is associated with PTB and stillbirth. However, while hospitalization for obstetric complications mirrors a high-risk pregnancy possibly leading to PTB independently of COVID-19\(^4\), hospitalization because of SARS-CoV-2 infection could be regarded as a surrogate marker for the severity of COVID-19. The impact of hospitalization rate for SARS-CoV-2 on risk of PTB and stillbirth suggests that the severity of infection is also eminent contradictory to previous reports \(^2\).

Women with a symptomatic SARS-CoV-2 infection could profit most from an intensive obstetric surveillance. A symptomatic SARS-CoV-2 infection increased pregnancy complications and should be prevented by vaccination.
References


**Author Contributions:** AI designed and conducted the analyses reported in this study and wrote the manuscript. BS contributed significantly to the design of these analyses. ES and UP contributed significantly to the final draft of this manuscript by discussing the results and their interpretations and by revising earlier drafts. NM provided significant data for the analysis. UP is one of the principal investigators of the CRONOS Network. All authors contributed to the interpretation of results, revised the paper draft and approved the final manuscript.

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Conflict of Interest
All authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stillbirth (all patients)</th>
<th>Early PTB (only live births)</th>
<th>Late PTB (only live births)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI  p</td>
<td>RR 95% CI  p</td>
<td>RR 95% CI  p</td>
</tr>
<tr>
<td>Maternal age (per year increase)</td>
<td>0.98 0.91 – 1.06 0.618</td>
<td>1.05 0.99 – 1.12 0.096</td>
<td>1.01 0.99 – 1.04 0.266</td>
</tr>
<tr>
<td>History of miscarriage/preterm delivery</td>
<td>4.97 1.38 – 17.98 0.014</td>
<td>1.22 0.19 – 7.98 0.837</td>
<td>1.76 1.06 – 2.91 0.027</td>
</tr>
<tr>
<td>In-patient care due to SARS-COV-2 infection</td>
<td>16.62 3.34 – 82.54 0.001</td>
<td>12.97 5.37 – 31.33 &lt;0.001</td>
<td>3.99 2.77 – 5.77 &lt;0.001</td>
</tr>
<tr>
<td>In-patient care due to other obstetric complications</td>
<td>25.49 5.82 – 111.60 &lt;0.001</td>
<td>7.63 3.09 – 18.83 &lt;0.001</td>
<td>5.27 3.78 – 7.36 &lt;0.001</td>
</tr>
<tr>
<td>Early (1st and 2nd trimester) vs. late (3rd trimester) infection</td>
<td>2.76 1.15 – 6.64 0.023</td>
<td>2.07 1.10 – 3.91 0.025</td>
<td>0.60 0.44 – 0.81 0.001</td>
</tr>
</tbody>
</table>

Table 1: Multivariate log-binominal model analysis regarding the risk of stillbirth, early and late PTB according to the time point of SARS-CoV-2 infections (early versus late infection). Significant p-values are marked bold. RR adjusted for maternal age, SARS-CoV-2 infection needing in-patients’ treatment, obstetric reasons urging in-patients’ treatment and history of miscarriage/preterm delivery.
Figure 1(Supplements): Flow-diagram of the recruitment process of the final study cohort.

Assessed for eligibility (n=2650)

Excluded (n=1501)
- Did not meet inclusion criteria (n=1048)
  - No COVID-19 symptoms (n=709)
  - Infection after 37+0 Weeks (n=325)
  - Miscarriage before 20+0 weeks (n=14)
- Missing data (n=453)
  - Delivery date (n=314)
  - COVID-19 symptoms (n=129)
  - Stillbirth (n=7)
  - Previous miscarriage (n=2)
  - Maternal age (n=1)

Included (n=1149)

Live births (n=1128)

Stillbirths (n=21)