Is the risk of still and preterm birth affected by the timing of symptomatic SARS-CoV-2 infection during pregnancy? Data from the COVID-19 Related Obstetrics and Neonatal Outcome Study Network, Germany

OBJECTIVE: A SARS-CoV-2 infection during pregnancy increases the risk for preterm birth (PTB).1 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.2 This study aimed to analyze the association of the timing of symptomatic SARS-CoV-2 infection during pregnancy with PTB and stillbirth risk.

STUDY DESIGN: From April 3, 2020 to August 24, 2021, the data of 2650 women with a 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). The exclusion criteria were defined as follows: (1) asymptomatic infection, (2) SARS-CoV-2 infection after 37+0 weeks of gestation, (3) miscarriage before 20+0 weeks, and (4) incomplete data in terms of infection or delivery date, live birth, maternal age, admission for SARS-CoV-2 symptoms or for obstetrical reasons or a history of stillbirth or PTB in previous pregnancies. The timing of exposure was dichotomized into early (first or second trimester) and late (third trimester) infections. The primary endpoints were PTB (classified as early PTB ≤32 weeks’ gestation or late PTB >32 weeks’ gestation) 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 and occurrence of other pregnancy complications. For categorical variables, chi-Square or Fisher exact tests (n<5) were used. All statistical analyses were performed using SPSS (version 27) for Windows (IBM Corp, Armond, NY).

RESULTS: A total of 1149 patients were eligible for the final analysis. Of those, 1128 (98.2%) had a live birth and of those, 201 (17.8%) were preterm (Supplemental Figure). A total of 21 (1.8%) stillbirths occurred (Supplemental Table). More than half of the analyzed women acquired the infection in the third trimester and 45.5% acquired it earlier in pregnancy. The timing of exposure was dichotomized into early (first or second trimester) and late (third trimester) infections. The primary endpoints were PTB (classified as early PTB ≤32 weeks’ gestation or late PTB >32 weeks’ gestation) 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 and occurrence of other pregnancy complications. For categorical variables, chi-Square or Fisher exact tests (n<5) were used. All statistical analyses were performed using SPSS (version 27) for Windows (IBM Corp, Armond, NY).

Early symptomatic SARS-CoV-2 infection increased the risk for early PTB (aRR, 2.07; 95% CI, 1.10–3.91) and stillbirth (aRR, 2.76; 95% CI, 1.15–6.64) when compared with a late infection (Table). The risk for PTB was higher within 4 weeks after infection (RR, 4.89; 95% CI, 3.86–6.19). Threatened PTB (RR, 1.80; 95% CI, 1.07–3.01) and

<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>RR</td>
<td>95% CI</td>
<td>P value</td>
<td>RR</td>
</tr>
<tr>
<td>Maternal age (per year increase)</td>
<td>0.98</td>
<td>0.91–1.06</td>
<td>.618</td>
</tr>
<tr>
<td>History of miscarriage or preterm delivery</td>
<td>4.97</td>
<td>1.38–17.98</td>
<td>.014*</td>
</tr>
<tr>
<td>In-patient care for SARS-COV-2 infection</td>
<td>16.62</td>
<td>3.34–82.54</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>In-patient care for other obstetrical complications</td>
<td>25.49</td>
<td>5.82–111.60</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Early (1st and 2nd trimester) vs late (3rd trimester) infection</td>
<td>2.76</td>
<td>1.15–6.64</td>
<td>.023*</td>
</tr>
</tbody>
</table>

RR adjusted for maternal age, SARS-CoV-2 infection needing in-patients’ treatment, obstetrical reasons urging in-patients’ treatment and history of miscarriage or preterm delivery.
CI, confidence interval; PTB, preterm birth; RR, risk ratio.
* Indicates significant P values.

gestational cholestasis (RR, 3.18; 95% CI, 1.19–8.44) occurred more often in late infections.

CONCLUSION: A total of 17.8% of the women with symptomatic infections delivered preterm—more than double the rate when compared with the general German preterm birth rate of nearly 9%. Hospitalization for any reason was associated with PTB and stillbirth. However, although hospitalization for obstetrical complications mirrors a high-risk pregnancy possibly leading to PTB independently of COVID-19, hospitalization because of SARS-CoV-2 infection could be regarded as a surrogate marker for the severity of COVID-19. The impact of the hospitalization rate for SARS-CoV-2 on the risk for PTB and stillbirth suggests that the severity of infection is also contradictory to previous reports.

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

ACKNOWLEDGMENT
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This study was registered with the German Clinical Trials Register under identifier DRKS00021208; URL: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00021208).

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REFERENCES
SUPPLEMENTAL FIGURE
Flow diagram of 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)

## Baseline characteristics of the study cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early infection (n = 523, 45.5%)</th>
<th>Late infection (n = 626, 54.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td>% or SD</td>
<td>% or SD</td>
</tr>
<tr>
<td>In-patient care for SARS-COV-2 infection</td>
<td>31.47 (range, 1–27)</td>
<td>31.2 (range, 38–37)</td>
</tr>
<tr>
<td>In-patient care for obstetrical complications</td>
<td>96</td>
<td>129</td>
</tr>
<tr>
<td>Vaccinateda</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>History of miscarriage or preterm delivery</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Timing of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at infection (wk, all patients)</td>
<td>18.65 (range, 1–27)</td>
<td>33.0 (range, 38–37)</td>
</tr>
<tr>
<td>Gestational age at delivery (wk, all patients)</td>
<td>39.01</td>
<td>38.77</td>
</tr>
<tr>
<td>Gestational age at delivery (wk, only live births; n=1128)</td>
<td>39.26 (range, 38–37)</td>
<td>38.80 (range, 38–37)</td>
</tr>
<tr>
<td>Preterm ≤37+0 wk</td>
<td>17.8%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Preterm early ≤32+0 wk</td>
<td>3.3%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Preterm late 32+1 to 37+0 wk</td>
<td>14.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Pregnancy complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive pregnancy disorders</td>
<td>4.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>1.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Suspicious fetal heart rate pattern</td>
<td>5.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>10.0%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Premature labor with need of therapy</td>
<td>5.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Gestational cholestasis</td>
<td>2.1%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Data are presented for a sample of n=1149 patients.

HELP: hemolysis, elevated liver enzymes, low platelet count; SD, standard deviation.

*a Data available for 1034 pregnant women; 3 vaccinations after infection; ^A total of 126 (62.7%) patients were iatrogenic. In 35 cases (17.4 %), COVID-19 was the reason for delivery. In 91 (45.3%) cases, delivery was for obstetrical reasons.