ORIGINAL RESEARCH ARTICLE

SARS-CoV-2 infection in pregnancy in Denmark—characteristics and outcomes after confirmed infection in pregnancy: A nationwide, prospective, population-based cohort study

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Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; DCOD, the Danish COVID-19 in pregnancy database; DNPR, The Danish National Patient Register; GA, gestational age in completed weeks; ICU, intensive care unit; LMP, date of the first day of the last menstrual period; MiBa, Danish Microbiology Database; NICU, neonatal intensive care unit; OR, crude odds ratio; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

Introduction: Assessing the risk factors for and consequences of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy is essential to guide clinical care. Previous studies on SARS-CoV-2 infection in pregnancy have been among hospitalized patients, which may have exaggerated risk estimates of severe outcomes because all cases of SARS-CoV-2 infection in the pregnant population were not included. The objectives of this study were to identify risk factors for and outcomes after SARS-CoV-2 infection in pregnancy independent of severity of infection in a universally tested population, and to identify risk factors for and outcomes after severe infection requiring hospital admission.

Material and methods: This was a prospective population-based cohort study in Denmark using data from the Danish National Patient Register and Danish Microbiology Database and prospectively registered data from medical records. We included all pregnancies between March 1 and October 31, 2020 and compared women with a positive SARS-CoV-2 test during pregnancy to non-infected pregnant women. Cases of SARS-CoV-2 infection in pregnancy were both identified prospectively and through register linkage to ensure that all cases were identified and that cases were pregnant during infection. Main outcome measures were pregnancy, delivery, maternal, and neonatal outcomes. Severe infection was defined as hospital admission due to coronavirus disease 2019 (COVID-19) symptoms.

Results: Among 82,682 pregnancies, 418 women had SARS-CoV-2 infection during pregnancy, corresponding to an incidence of 5.1 per 1000 pregnancies, 23 (5.5%) of which required hospital admission due to COVID-19. Risk factors for infection were asthma (odds ratio [OR] 2.19, 95% CI 1.41–3.41) and being foreign born (OR 2.12, 95% CI 1.70–2.64). Risk factors for hospital admission due to COVID-19 included obesity (OR 2.74, 95% CI 1.00–7.51), smoking (OR 4.69, 95% CI 1.58–13.90), infection after gestational age (GA) 22 weeks (GA 22–27 weeks: OR 3.77, 95% CI 1.16–12.29; GA 28–36 weeks: OR 4.76, 95% CI 1.60–14.12), and having asthma (OR 4.53, 95% CI 1.39–14.79). We found no difference in any obstetrical or neonatal outcomes. Severe infection was defined as hospital admission due to coronavirus disease 2019 (COVID-19) symptoms.

Conclusions: Only 1 in 20 women with SARS-CoV-2 infection during pregnancy required admission to hospital due to COVID-19. Risk factors for admission comprised obesity, smoking, asthma, and infection after GA 22 weeks. Severe adverse outcomes of SARS-CoV-2 infection in pregnancy were rare.

Keywords: cohort studies, coronavirus disease 2019, obstetric delivery, pregnancy complications, pregnancy outcome, prospective studies, severe acute respiratory syndrome coronavirus 2
INTRODUCTION

The World Health Organization declared a global pandemic of coronavirus disease 2019 (COVID-19) in March 2020. COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Assessing the risk factors for and consequences of infection with SARS-CoV-2 during pregnancy is essential to guide clinical guidelines and care.

Most previous population-based studies on SARS-CoV-2 infection in pregnancy have been among hospitalized patients, which may exaggerate the risk estimates of severe outcomes because not all cases of SARS-CoV-2 infection in the pregnant population were included. Only one study from the Netherlands included all cases independent of severity and hospital admission. However, in that study, cases were identified prospectively in obstetric clinics, with the risk of selection bias. Additionally, the outcomes are in most studies compared with outcomes of historic cohorts of non-infected women, with the risk that the consequences of the pandemic will be attributed solely to SARS-CoV-2. Lastly, testing strategies influence the estimated prevalence of SARS-CoV-2 infection, and potentially also the estimated severity of outcomes, if mild and asymptomatic cases are also detected.

The testing strategy in Denmark rapidly evolved during the pandemic from testing the most ill in March 2020 to testing individuals with mild symptoms from April and testing close contacts from May. Universal testing of all pregnant women admitted to hospital including for delivery was implemented nationwide in early May 2020.

The objectives of this study were to identify risk factors for SARS-CoV-2 infection in pregnancy in a universally tested population and risk factors for severe infection requiring hospital admission, and to investigate the consequences of infection and severe infection on pregnancy, delivery, and neonatal outcomes when comparing with all non-infected pregnancies during the same time period.

MATERIAL AND METHODS

This was a nationwide prospective population-based study investigating the association between SARS-CoV-2 infection in pregnancy and clinical characteristics and maternal, delivery, and neonatal outcomes. The study used prospectively registered data from medical records registered in the Danish COVID-19 in pregnancy database (DCOD) and register data obtained from the following national registers: the Danish National Patient Register (DNPR), the Danish Microbiology Database (MiBa), and the Civil Registration System.

The overall study population was identified in DNPR and comprised all women registered with a pregnancy or birth-related International Classification of Diseases 10th revision diagnosis or procedure between March 1 and October 31, 2020 as specified in the Supporting Information Table S1. SARS-CoV-2-positive cases within the study population were identified by linkage to MiBa. In Denmark, all positive polymerase chain reaction (PCR) tests are registered in MiBa, but antigen and antibody tests were not during the study period. Pregnant women identified in the registers were followed up until December 11, 2020 considering all outcomes.

In the DCOD, women with a positive SARS-CoV-2 test during pregnancy between March 1 and October 31, 2020 were registered prospectively. Eligible SARS-CoV-2 tests included (a) PCR tests (of pharyngeal swab or tracheal secretion), (b) antigen tests (of nasal swab), or (c) detection of antibodies (IgG or total antibodies in serum) combined with a history of COVID-19 symptoms during pregnancy. The antibody assays used in Denmark have a high specificity and the risk of false positives is low; a positive test was therefore considered inclusive. All obstetric units in Denmark reported to the DCOD based on data from prospectively collected medical records. DCOD was based in EasyTrial (easytrial.net, Denmark). To secure data completeness, cases were validated every second month by register linkage, with data obtained from the DNPR, Danish National Health Service Register, and MiBa. The validation data set included only personal identification number, date of positive SARS-CoV-2 PCR test, date of hospital contact, and name of the hospital. Non-reported cases identified by validation who were pregnant at the time of a positive SARS-CoV-2 PCR test were entered into the DCOD retrospectively. Women included in the DCOD were followed up until data extraction on February 8, 2021.

The register data on the overall study population were pseudonymized, making it impossible to validate the SARS-CoV-2-positive cases from the registers against the DCOD cases on an individual level. We therefore present data for SARS-CoV-2-positive women from the DCOD alongside cases identified in the registers to illustrate the degree of comparability. SARS-CoV-2 cases in the DCOD and those registered in the national registers were each compared with the non-infected population. The validity of maternal and neonatal characteristics, surgical procedures, and main diagnoses in the Danish registers is considered high, and we therefore evaluated that a comparison between the DCOD data and the register data was relevant.

The estimated date of delivery was registered in the DCOD and based on the first-trimester ultrasound examination offered to all pregnant women between gestational age (GA) 11 and 14 completed weeks. In case of first-trimester abortion, the estimated date of delivery was calculated based on the GA at abortion. In the DCOD, date of the first day of the last menstrual period (LMP) was defined as estimated date of delivery minus 280 days. In the register data, the LMP was calculated based on the registered GA at delivery or abortion. If still pregnant, we calculated the LMP based on GA at ultrasound examination, and if missing, the recommended GA for the registered ultrasound examinations. For abortions with a missing
registration of GA, GA was imputed based on the mean GA within the
categories miscarriage or induced abortion.

Characteristics included maternal age at LMP, pre-pregnancy
body mass index (BMI) based on the height and pre-pregnancy
weight registered at first contact in pregnancy, smoking defined as
any smoking during pregnancy, parity, multiple pregnancy, pre-
eclampsia, gestational diabetes, and diabetes. The register data
set also included pre-existing asthma and hypertension diagnosed
within 5 years of LMP. Supporting information Table S2 presents the
codes used to identify characteristics and outcomes in DNPR. The
DCOD also included information on migrant status defined as not
born in Denmark, employment status including ongoing education,
asthma defined as asthma requiring steroid inhalation as registered
in the Danish Shared Medication Record,16 pre-existing medical
problems and previous pregnancy-related complications as specified
in Supporting information Table S3. GA at infection was calculated
based on the date of the first positive SARS-CoV-2 test in the case
of a PCR test or date of symptoms in the case of an antibody test.

Maternal outcomes included admission to an ICU, pneumonia (in
the DCOD defined as confirmed by radiologic examination), throm-
boembolic events, maternal mortality (death during pregnancy or
within 7 days postpartum) and pregnancy outcomes including de-
elivery, termination of pregnancy before GA 23 weeks, or miscarriage
before GA 22 weeks.

Delivery outcomes comprised mode of delivery, induction of
labor, and preterm birth before GA 37 weeks.

Neonatal outcomes included admission to a NICU directly from
the delivery or maternity ward, stillbirth from GA 22 weeks, Apgar
score at 5 minutes, umbilical artery pH, and neonatal death (within
28 days postpartum).

Information on maternal and neonatal death was retrieved from
the Danish Civil Registration System, which is considered highly
valid and complete.12

Data on migrant status and infant admission to a NICU were
not available in our register data. These variables registered in the
DCOD were therefore compared with historical data comprising mi-
grant status of all women with a liveborn child in 2019 as reported
by Statistics Denmark17 and admissions to an NICU of all live-born
children in 2019 as reported by the Danish Quality Database for
newborns.18

In the DCOD, admission to hospital with a concurrent SARS-
CoV-2 infection was defined as admission and discharge on two dif-
f erent dates and a positive SARS-CoV-2 test within 14 days before
or during admission. Severe infection was defined if admission to
hospital was due to COVID-19 symptoms.

2.1 Statistical analyses

Categorical variables are presented as count with percentage, and
continuous variables as median with interquartile range. For DCOD
data numbers less than 3 and for register data numbers less than 5
are not reported to avoid identification according to the respective
ethical approvals. The categorical DCOD data were analyzed with
chi-squared test when compared with the non-infected popula-
tion, and with logistic regression when comparing severe and
non-severe DCOD cases including multivariate analyses adjusting
for the predefined risk factors age, BMI, parity, and smoking. Continuous DCOD variables were analyzed using the Wilcoxon
signed rank test. We performed a sub-analysis of the DCOD cases
testing for the influence of GA at time of SARS-CoV-2 infection
on key outcomes comprising cesarean delivery, induction of labor,
preterm birth, and NICU admission. In the analysis of register data,
categorical outcomes were assessed with univariate and multiple
logistic regression and continuous variables with linear regression.
The multivariate analyses adjusted for (a) maternal age and LMP
to adjust for time of inclusion in the study, and (b) predefined risk
factors including maternal age, LMP, parity, BMI, and smoking. In
the linear regression model, we included log-transformed outcome
variables, applying bootstrapping to account for non-normal dis-
tribution of residuals. For the outcomes miscarriage, termination
of pregnancy, and preterm delivery, a Cox regression analysis was
performed, including SARS-CoV-2 as time-dependent exposure,
to account for duration of exposure to SARS-CoV-2 during follow
up. These analyses were performed with delayed entry to reduce
the risk of immortal-time bias, which can occur when participants
cannot experience the outcome during part of the follow-up time.
For the first two outcomes, women were therefore included in the
survival analysis according to the time of first registered hospital
contact, and for preterm delivery, women were included at GA
100 days. SARS-CoV-2 exposure was registered at the date of posi-
tive test. Missing data were excluded from all analyses. A p-value
of 0.05 or less was considered statistically significant. Data were
analyzed using Stata/MP16 (64-bit; StataCorp) and SPSS statistics
27 (IBM).

2.2 Ethical approval

The study was approved by the Danish Patient Safety Authority on
April 24, 2020 (reg. no. 31-1521-252), the regional Data Protection
Agency in Region Zealand on March 23, 2020 (reg. no. REG-
022-2020), and the regional Data Protection Agency in the Region
of Southern Denmark on April 15, 2020 (reg. no. 20/17416). Individual
patient consent was not required. The study is reported according to
STROBE guidelines.19

3 RESULTS

Among 82,682 pregnancies in Denmark between March 1 and
October 31, 2020, 420 women had a SARS-CoV-2 positive PCR test,
and 418 SARS-CoV-2 cases were confirmed as being during preg-
nancy through validation against medical records. Figure 1A illus-
trates the flow through the register-based study, and Figure 1B the
flow through the DCOD study.
The overall incidence of SARS-CoV-2 infection during validated pregnancy in the inclusion period was 5.1 (95% CI 4.7–5.5) per 1000 pregnancies, with the monthly incidence ranging from 0.2 per 1000 pregnancies in July to 3.8 per 1000 pregnancies in October (Supporting Information Figure S1). Of the SARS-CoV-2 cases in pregnancy, 23 (5.5%) were admitted to hospital because of COVID-19 symptoms. The risk of pneumonia was significantly higher among SARS-CoV-2-infected pregnant women (OR 15.97, 95% CI 6.92–36.86). All cases of pneumonia (n = 6) were among women admitted to hospital because of COVID-19 and none of them smoked in pregnancy. The rate of thromboembolic events and admission to an ICU was low, and we had no cases of maternal death during the study period. The rate of early pregnancy loss did not vary between the groups after adjusting for exposure time. However, the risk of termination of pregnancy was increased after adjustment (hazard ratio 2.39, 95% CI 1.29–4.45) for exposure time. There were no neonatal deaths among the children of SARS-CoV-2-infected women. The median time between SARS-CoV-2 infection and delivery was 88 days (interquartile range 35–138). We found no difference between the groups regarding any of the delivery or infant outcomes. Adjustment did not change the results. There were no neonatal deaths among the children of SARS-CoV-2-infected women.

The outcomes of the SARS-CoV-2-infected women compared with all non-infected pregnancies are presented in Table 2. The risk of pneumonia was significantly higher among SARS-CoV-2-infected pregnant women (OR 15.97, 95% CI 6.92–36.86). All cases of pneumonia (n = 6) were among women admitted to hospital because of COVID-19 and none of them smoked in pregnancy. The rate of thromboembolic events and admission to an ICU was low, and we had no cases of maternal death during the study period. The rate of early pregnancy loss did not vary between the groups after adjusting for exposure time. However, the risk of termination of pregnancy was increased after adjustment (hazard ratio 2.39, 95% CI 1.29–4.45) for exposure time. There were no neonatal deaths among the children of SARS-CoV-2-infected women.

We found no statistically significant differences in outcomes between women requiring hospital admission due to COVID-19 symptoms compared with less severe SARS-CoV-2 cases (Table 3).

There was no difference in risk of cesarean delivery, induction of labor, preterm birth, or NICU admission in relation to GA at infection among the SARS-CoV-2-infected women (data not shown).
| Basic characteristics | SARS-CoV-2-infected pregnant women identified in DCOD | SARS-CoV-2-infected pregnant women/ pregnancies identified in the national registers | Non-infected pregnancies identified in the national registers | SARS-CoV-2-infected vs. non-infected pregnancies | SARS-CoV-2-infected women identified in DCOD | Women requiring hospital admission due to COVID-19 symptoms vs. women with uncomplicated SARS-CoV-2 infection | \( p \) |
|-----------------------|----------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------|------|
| **Age (years)**       | 418 (12.2)                                        | 420 (11.4)                                      | 23 (12.6)                                      | 1 (ref.)                                      | 23 (1.02)                                     | 1.00 (0.75–1.41)                                                                 | 0.99 |
| <25                   | 51 (11.0)                                         | 48 (11.4)                                       | 10324 (12.6)                                   | 1 (ref.)                                      | 10 (43.5)                                     | 29.9 (25.4–33.2)                                                                | 0.87 |
| 25–34                 | 291 (69.6)                                        | 297 (70.7)                                      | 57372 (69.7)                                   | 1.11 (0.82–1.51)                              | 185 (47.0)                                    | 29.5 (27.0–33.5)                                                               | 0.75 |
| ≥35                   | 76 (18.2)                                         | 75 (17.9)                                       | 14566 (17.7)                                   | 1.11 (0.77–1.59)                              | 14 (61.5)                                     | NA                                                                            | 0.018|
| ≥30                   | 76 (18.2)                                         | 75 (17.9)                                       | 14566 (17.7)                                   | 1.11 (0.77–1.59)                              | 14 (61.5)                                     | NA                                                                            | 0.018|
| Median                | 29.6 (27.0–33.0)                                  | 29.0 (27.0–33.0)                                | 30.0 (27.0–33.0)                               | NA                                            | 29.9 (25.4–33.2)                                                                | 0.87 |
| BMI (kg/m\(^2\))     | 241 (60.3)                                        | 113 (55.1)                                      | 27083 (58.5)                                   | 1 (ref.)                                      | 10 (43.5)                                     | 29.9 (25.4–33.2)                                                                | 0.87 |
| <25 (normal)          | 241 (60.3)                                        | 113 (55.1)                                      | 27083 (58.5)                                   | 1 (ref.)                                      | 10 (43.5)                                     | 29.9 (25.4–33.2)                                                                | 0.87 |
| 25–29.9 (overweight) | 93 (23.3)                                         | 61 (29.8)                                       | 11904 (25.7)                                   | 0.88 (0.68–1.12)                              | 6 (26.1)                                      | 26.1 (27.0–33.0)                                                               | 1.60 |
| ≥30 (obese)           | 44 (11.0)                                         | 23 (11.2)                                       | 4609 (9.9)                                     | 1.07 (0.75–1.48)                              | 7 (30.4)                                      | 59 (15.6)                                                                     | 2.74 |
| Median                | 24.1 (26.9–33.4)                                  | 24.0 (22.0–27.0)                                | 24.0 (21.0–27.0)                               | NA                                            | 25.6 (23.7–31.2)                                                                | 24.0 |
| Smoking Smoking in pregnancy | 27 (6.8)                                         | 10 (4.9)                                        | 3598 (7.9)                                     | 0.86 (0.58–1.27)                              | 5 (22.7)                                      | 22 (5.9)                                                                      | 4.69 |
| Unknown               | 23 (5.5)                                         | 214 (51.0)                                      | 36478 (44.3)                                   | 2.19 (1.41–3.41)                              | 4 (17.4)                                      | 17 (4.4)                                                                      | 4.53 |
| Pre-existing asthma   | 21 (5.2)                                         | 23 (5.5)                                        | 1996 (2.4)                                     | 2.19 (1.41–3.41)                              | 4 (17.4)                                      | 17 (4.4)                                                                      | 4.53 |
| Unknown               | 12 (2.9)                                         | 12 (2.9)                                        | NA                                            | 2.19 (1.41–3.41)                              | 4 (17.4)                                      | 17 (4.4)                                                                      | 4.53 |

(Continues)
TABLE 1 (Continued)

|                          | SARS-CoV-2-infected pregnant women identified in DCOD | SARS-CoV-2-infected pregnant women/pregnancies identified in the national registers\(a\) | Non-infected pregnancies identified in the national registers\(a\) | SARS-CoV-2-infected vs. non-infected pregnancies | SARS-CoV-2-infected women identified in DCOD |
|--------------------------|-------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------|---------------------------------------------|
|                          | \(N = 418\)                                           | \(N = 420\)                                                                     | \(N = 82\,262\)                                                 | \(OR_D (95\% \text{ CI})\)                    | \(OR_D (95\% \text{ CI})\)                |
| Pre-existing medical problem\(c\) | Unknown                                               | 82 (20.2)                                                                       | NA                                                              | NA                                            | 8 (34.8)                                    |
|                          |                                                       | NA                                                                               | NA                                                              | 74 (19.3)                                     |
|                          |                                                       | 12 (2.9)                                                                        | NA                                                              | 12 (3.0)                                      | 2.23 (0.91–5.45)                           |
| Migrant\(d\)            |                                                       | 119 (32.2)                                                                      | NA                                                              | 11,211 (18.3)                                 |
|                          |                                                       | 2.12 (1.70–2.64)                                                                | NA                                                              | 10 (47.6)                                     |
|                          |                                                       | Unknown                                                                         | 49 (11.7)                                                       | 2 (8.7)                                       |
|                          |                                                       | 47 (11.9)                                                                       | 109 (31.3)                                                     | 1.99 (0.82–4.83)                             |
| COVID-19 characteristics  |                                                       |                                                                                   |                                                                 |                                               |
| GA at infection\(e\)    | <22                                                   | 191 (45.8)                                                                      | 211 (50.2)                                                     | NR                                            |
|                          | 22–27                                                 | 76 (18.2)                                                                       | 77 (18.3)                                                      | NR                                            |
|                          | 28–36                                                 | 97 (23.3)                                                                       | 89 (21.2)                                                      | NR                                            |
|                          | 37–                                                   | 53 (12.7)                                                                       | 43 (10.2)                                                      | NR                                            |
|                          | Unknown                                               | 1 (0.2)                                                                         | 21⁰ week (14⁰–29⁰ week)                                        | NR                                            |
|                          | Median                                                | 22⁰ week (15⁰–30⁰ week)                                                         | 21⁰ (14⁰–29⁰ week)                                             | NR                                            |
|                          |                                                       | 26⁰ week (23⁰–32⁰ week)                                                         | 22⁰ (14⁰–30⁰ week)                                             | 0.093                                         |
| Test type                | PCR or antigen test                                   | 399 (97.3)                                                                      | 420 (100)                                                     | NR                                            |
|                          | Antibodies (IgG or total) in serum                    | 11 (2.7)                                                                        | NR                                                              | 23 (10)                                       |
|                          | Unknown                                               | 8 (1.9)                                                                         | 8 (2.0)                                                        | 0 (0)                                         |

Pregnancy characteristics

(Continues)
TABLE 1 (Continued)

| SARS-CoV-2-infected pregnant women identified in DCOD | SARS-CoV-2-infected pregnant women/pregnancies identified in the national registers\(a\) | Non-infected pregnancies identified in the national registers\(a\) | SARS-CoV-2-infected vs. non-infected pregnancies | SARS-CoV-2-infected women identified in DCOD |
|------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|---------------------------------------------|
| \(N = 418\)                                          | \(N = 420\)                                                                       | \(N = 82262\)                                                   | \(OR_D(95\%\ CI)\)                               | \(OR_R(95\%\ CI)\)                         |
| Parity                                               |                                                                                   |                                                                 |女性 |                                                                 |
| Multiparous                                          | 230 (56.7)                                                                        | 218 (53.7)                                                      | 39727 (55.1) | 1.07 (0.88–1.30)                     | 0.95 (0.78–1.15)                           |
| Unknown                                              | 12 (2.9)                                                                          | 14 (3.3)                                                        | 10156 (12.3) | 0.52 (0.35–0.78)                     | 1.06 (0.79–1.44)                           |
| Multiple pregnancy                                   |                                                                                   |                                                                 |女性 |                                                                 |
| Known                                                | <3                                                                                 | <5                                                              | NA                                  | NA                                  | NA                                  |
| Unknown                                              | 4 (1.0)                                                                           | 6 (1.4)                                                         | 1642 (2.0) | NA                                  | 0.71 (0.50–0.99)                           |
| Pre-eclampsia/Eclampsia                             |                                                                                   |                                                                 |女性 |                                                                 |
| Known                                                | <3                                                                                 | 6 (1.4)                                                         | NA                                  | NA                                  | NA                                  |
| Unknown                                              | 4 (1.0)                                                                           | 6 (1.4)                                                         | 1642 (2.0) | 0.71 (0.50–0.99)                     | 1.00 (0.76–1.31)                           |
| GDM                                                  | 19 (4.5)                                                                          | 22 (5.2)                                                        | 3353 (4.1) | 1.12 (0.71–1.78)                     | 1.30 (0.85–2.00)                           |
| Thromboembolic event                                 |                                                                                   |                                                                 |女性 |                                                                 |
| Known                                                | <3                                                                                 | 0 (0.0)                                                         | 62 (0.1) | NA                                  | 0 (0)                                  | 0 (0)                                    | 1.76 (0.71–4.39) |
| Unknown                                              | 4 (1.0)                                                                           | 6 (1.4)                                                         | 1642 (2.0) | <3                                  | 0 (0)                                  | 1.76 (0.71–4.39) |

Note: Data are presented as count (%) or median (interquartile range). Significant results are highlighted in bold type.

\(OR_D\) was estimated using 2 × 2 contingency tables. \(OR_R\) was for categorical outcomes estimated using univariate logistic regression with the lowest value as the reference. \(OR_R\) was for continuous variables estimated using linear regression with the dependent variable log-transformed and the unexposed category as reference. \(OR_{DCOD}\) was estimated using logistic regression.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; DCOD, Danish COVID-19 in pregnancy database; GA, gestational age; GDM, gestational diabetes mellitus; NA, not available; NR, not relevant; OR, odds ratio; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\(a\)The Danish national registers comprised the Danish National Patient Register (DNPR) and the Danish Microbiology Database (MiBa).

\(b\)Uncomplicated COVID-19 included cases where women did not require admission to hospital due to COVID-19 symptoms, and therefore included women in home isolation or women admitted for obstetrical reason within 14 days of first positive SARS-CoV-2 test or symptoms.

\(c\)Pre-existing medical problems included endocrine, cardiac, renal, psychiatric, hematological, inflammatory and autoimmune disease, and cancer and HIV.

\(d\)Migrant was defined as not born in Denmark. The comparator group was all women with a live-born child in 2019 in Denmark \(N = 61,167\) (Statistics Denmark, https://statistikbanken.dk/FODIE [accessed February 4, 2021]). Country of origin is specified in Supporting Information, Table S4.

\(e\)GA at infection was defined as date of first positive test in case of a PCR test or date of symptoms in case of an antibody test.
TABLE 2  Outcomes for women with SARS-CoV-2 infection in pregnancy compared to all pregnancies in Denmark between March 1 and October 31, 2020

| Maternal outcome                              | SARS-CoV-2-infected pregnant women identified in DCOD | SARS-CoV-2-infected pregnant women/ pregnancies identified in the national registers | Non-infected pregnancies identified in the national registers | SARS-CoV-2-infected vs. non-infected pregnancy<sup>a</sup> |
|------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|
|                                                 | OR<sub>D</sub> (95% CI)                               | OR<sub>R</sub> (95% CI)                                                             | HR<sub>a</sub> (95% CI)                                     |                                                          |
| Maternal outcome                              |                                                      |                                                                                     |                                                             |                                                          |
| N = 418                                        | N = 420                                              | N = 82 262                                                                          |                                                             |                                                          |
| Pneumonia confirmed by radiologic examination  | 6 (1.5)                                              | <5                                                                                  | 77 (0.1)                                                   | 15.97 (6.92–36.86)                                        | NA                                                      |
| Unknown                                        | 11 (2.6)                                             |                                                                                     |                                                             |                                                          |
| Admission<sup>b</sup> to hospital due to COVID-19 | 23 (5.5)                                             | NA                                                                                  | NA                                                         | NA                                                      |
| Admission<sup>b</sup> to hospital for any reason | 65 (15.5)                                            | NA                                                                                  | NA                                                         | NA                                                      |
| Admission to intensive care unit               | <3                                                  | <5                                                                                  | 264 (0.3)                                                 | NA                                                      |
| Unknown                                        | 33 (7.9)                                             |                                                                                     |                                                             |                                                          |
| Death                                          | 0 (0)                                                | 0 (0.0)                               | 0 (0.0)                                                   | NA                                                      |
| Unknown                                        | 62 (14.8)                                            |                                                                                     |                                                             |                                                          |
| Early pregnancy loss GA <22 weeks             | 11 (2.7)                                             | 11 (2.6)                              | 6478 (7.9)                                               | NR                                                      |
| Unknown                                        | 7 (1.7)                                              |                                                                                     |                                                             |                                                          |
| GA <12 weeks                                  | 6 (1.5)                                              | >5                                                                                  | 4736 (5.8)                                               | NR                                                      |
| GA 12–21 weeks                                | 4 (1.0)                                              | <5                                                                                  | 1742 (2.1)                                               | NA                                                      |
| Missing information about GA                  | 1 (0.2)                                              |                                                                                     |                                                             |                                                          |
| Ectopic pregnancy                             | 3 (0.7)                                              | <5                                                                                  | 512 (0.6)                                               | 1.15 (0.37–3.61)                                        | NA                                                      |
| Termination of pregnancy                      | 11 (2.7)                                             | 10 (2.4)                              | 5261 (6.4)                                               | NR                                                      |
| Unknown                                        | 6 (1.4)                                              |                                                                                     |                                                             |                                                          |
| GA <12 weeks                                  | 6 (1.5)                                              | >5                                                                                  | 4929 (6.0)                                               | NR                                                      |
| GA 12–22 weeks                                | 5 (1.2)                                              | <5                                                                                  | 332 (0.4)                                               | NA                                                      |
| Delivery outcome                              |                                                      |                                                                                     |                                                             |                                                          |
| Delivered<sup>c</sup>                         |                                                      |                                                                                     |                                                             |                                                          |
| Mode of delivery                               |                                                      |                                                                                     |                                                             |                                                          |
| Vaginal                                        |                                                      |                                                                                     |                                                             |                                                          |
| N = 279                                        | N = 209                                              | N = 46 909                                                                          |                                                             |                                                          |
| Operative vaginal delivery                     | 221 (79.2)                                           | 169 (80.9)                            | 37 467 (79.9)                                           | 0.96 (0.72–1.28)                                        | 1.06 (0.75–1.50)                                        |
| Cesarean delivery (CD)                         | 18 (6.5)                                             | 13 (6.2)                              | 2583 (5.5)                                              | 1.18 (0.69–1.91)                                        | 1.14 (0.65–2.00)                                        |
| Emergency CD                                   | 58 (20.8)                                            | 40 (19.1)                             | 9442 (20.1)                                             | 1.04 (0.78–1.39)                                        |                                                          |
| Elective CD                                    | 35 (12.5)                                            | 26 (12.4)                             | 5368 (11.4)                                             | 1.11 (0.78–1.58)                                        | 1.10 (0.73–1.66)                                        |
| Induction                                      | 23 (8.2)                                             | 14 (6.7)                              | 3735 (8.0)                                              | 1.04 (0.68–1.59)                                        | 0.83 (0.48–1.43)                                        |

(Continues)
### TABLE 2 (Continued)

| SARS-CoV-2-infected pregnant women identified in DCOD | SARS-CoV-2-infected pregnant women/ pregnancies identified in the national registers | Non-infected pregnancies identified in the national registers | SARS-CoV-2-infected vs. non-infected pregnancy<sup>a</sup> |
|---|---|---|---|
| DCOD SARS-CoV-2 cases | Register SARS-CoV-2 cases | OR<sub>R</sub> (95% CI) | OR<sub>R</sub> (95% CI) | HR<sub>a</sub> (95% CI) |
| Preterm birth GA <37 weeks | 13 (4.7) | 12 (5.7) | 2539 (5.4) | 0.85 (0.49–1.49) | 1.06 (0.59–1.91) | 0.94 (0.47–1.88) |
| Median (IQR) | 40<sup>10</sup> weeks (39<sup>1</sup>-41<sup>0</sup> weeks) | 39<sup>6</sup> weeks (38<sup>6</sup>-40<sup>6</sup> weeks) | 40<sup>1</sup> weeks (39<sup>10</sup>-41<sup>0</sup> weeks) | NA | NA |
| Interval between COVID-19 and delivery (days), median (IQR) | 88 (35–138) | 76 (23–145) | NR | NA |

### Infant outcome

| IUFD | <3 | <5 | 134 (0.3) | NA | NA |
| Liveborn infants | N = 279 | N = 209 | 5714 (9.3) | 1.09 (0.74–1.61) |
| NICU admission<sup>b</sup> | 28 (10.0) | NA | NA |
| COVID-19 infection in neonate | 0 (0.0) | NA | NA |
| Congenital malformations | 5 (1.8) | NA | NA |
| Unknown | 26 (9.3) | NA | NA |
| Apgar at 5 min <7 | 0 (0) | <5 | 482 (1.0) | NR |
| Unknown | 3 (1.1) | <5 | 768 (1.6) |
| Median | 10 (10.0–10.0) | 10.0 (10.0–10.0) | 10.0 (10.0–10.0) | NA | 1.00 (1.00–1.00) |
| Umbilical cord pH (arterial) <7.10 | 8 (3.6) | 6 (3.8) | 1408 (4.6) | 0.77 (0.38–1.56) | 0.81 (0.36–1.84) |
| Unknown | 54 (19.4) | 49 (23.4) | 16 592 (35.0) |
| Median | 724 (7.18–7.27) | 7.2 (7.2–7.3) | 7.2 (7.2–7.3) | NA | 1.00 (1.00–1.00) |
| Neonatal death | 0 (0.0) | 0 (0.0) | 11 (0.0) | NA | NA |

Note: Data are presented as count (%) or median (interquartile range). Significant findings are highlighted in bold type.

Abbreviations: CD, cesarean delivery; COVID-19, coronavirus disease 2019; DCOD, Danish COVID-19 in pregnancy Database; GA, gestational age; GP, general practitioner; IQR, interquartile range; IUFD, intrauterine fetal death; NICU, neonatal intensive care unit; NR, not relevant; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>OR<sub>R</sub> was estimated using 2×2 contingency tables. OR<sub>R</sub> was for categorical outcomes estimated using univariate logistic regression with the lowest value as the reference. OR<sub>R</sub> was for continuous variables estimated using linear regression with the dependent variable log-transformed and the unexposed category as reference. HR<sub>a</sub> was estimated by a Cox regression adjusting for exposure time for relevant variables and the unexposed category as reference. HR<sub>a</sub> was adjusted for age and first day of the last menstrual period.

<sup>b</sup>Admission to hospital with a concurrent SARS-CoV-2 infection was defined as admission and discharge on two different dates and a positive SARS-CoV-2 test within 14 days of admission.

<sup>c</sup>The proportion of women who had delivered at the time of analyses varied due to different follow-up time in DCOD and the register data (please see Material and methods section).

<sup>d</sup>The comparator group were live-born children who were admitted to a neonatal intensive care unit directly from a delivery or maternity ward and later discharged home or who died among all live-born children in Denmark in 2019 (N = 59 391). (Dansk Kvalitetsdatabase for Nyfødte [DKN]). Datakvalitetsrapport 2019. Pg. 30. Available at: Microsoft Word – 2021-02-03 DKN_Datarapport_officiel (sundhed.dk [accessed February 19, 2021]).
## Table 3

Outcomes for women with severe COVID-19 infection requiring admission to hospital compared to less severe SARS-CoV-2 cases in pregnancy in Denmark between March 1 and October 31, 2020 as registered in the Danish COVID-19 in pregnancy database (DCOD)

| SARS-CoV-2-infected women registered in DCOD | Women requiring admission to hospital due to COVID-19 symptoms | Uncomplicated SARS-CoV-2 infection<sup>a</sup> | OR (95% CI) | p | aOR (95% CI)<sup>b</sup> |
|-----------------------------------------------|---------------------------------------------------------------|---------------------------------------------|-------------|---|----------------------|
| **Maternal outcome**                          |                                                               |                                             |             |   |                      |
| Death                                         |                                                               |                                             |             |   |                      |
| N = 23                                        | N = 395                                                       |                                             |             |   |                      |
| 0 (0)                                         | 0 (0)                                                         | NR                                          |             |   |                      |
| Unknown                                       | 1 (4.3)                                                       | 61 (15.4)                                   |             |   |                      |
| Ectopic pregnancy                             |                                                               |                                             |             |   |                      |
| 0 (0)                                         | 3 (0.8)                                                       | NR                                          |             |   |                      |
| Termination of pregnancy GA <23 weeks         |                                                               |                                             |             |   |                      |
| 0 (0)                                         | 11 (2.8)                                                      | NR                                          |             |   |                      |
| Unknown                                       | 0 (0)                                                         | 6 (1.5)                                     |             |   |                      |
| Delivered                                     |                                                               |                                             |             |   |                      |
| N = 23                                        | N = 395                                                       |                                             |             |   |                      |
| 17 (73.9)                                     | 262 (66.3)                                                    | 1.44 (0.55–3.73)                            | 1.74 (0.62–4.93) | 0.250 |                      |
| **Delivery outcome**                          |                                                               |                                             |             |   |                      |
| Delivered                                     |                                                               |                                             |             |   |                      |
| N = 17                                        | N = 262                                                       |                                             |             |   |                      |
| Unassisted vaginal delivery                   | 11 (64.7)                                                     | 192 (73.3)                                  | 1 (ref)     | 1.04 (0.39–2.77)     | 1.12 (0.40–3.15) |
| Operative vaginal delivery                    | 0 (0.0)                                                       | 18 (6.9)                                    | NR          | NR |                      |
| Emergency CD                                  | 3 (17.6)                                                      | 32 (12.2)                                   | 1.64 (0.43–6.19) | 1.88 (0.46–7.74) |                      |
| Elective CD                                   | 3 (17.6)                                                      | 20 (7.6)                                    | 2.62 (0.67–10.17) | 3.81 (0.85–17.09) |                      |
| Interval between COVID-19 and delivery (days) |                                                               |                                             |             |   |                      |
| N = 23                                        | N = 395                                                       |                                             |             |   |                      |
| 62 (42–103)                                   | 91 (35–138)                                                   | 0.250                                       |             |   |                      |
| **Infant outcome**                            |                                                               |                                             |             |   |                      |
| Liveborn infants                              |                                                               |                                             |             |   |                      |
| N = 17                                        | N = 262                                                       |                                             |             |   |                      |
| GA at delivery                                |                                                               |                                             |             |   |                      |
| 39<sup>15</sup> weeks (38<sup>4</sup>–40<sup>3</sup> weeks) | 40<sup>10</sup> weeks (39<sup>1</sup>–41<sup>0</sup> weeks) | 0.161                                   |             |   |                      |
| Preterm birth GA <37 weeks                    |                                                               |                                             |             |   |                      |
| <3                                             | >10                                                           | NA                                          |             |   |                      |
| NICU admission                                 |                                                               |                                             |             |   |                      |
| 4 (23.5)                                      | 24 (9.2)                                                      | 3.05 (0.92–10.10)                           | 3.37 (0.95–11.97) | 0.733 |                      |
| Gender                                        |                                                               |                                             |             |   |                      |
| Boy                                           |                                                               |                                             |             |   |                      |
| 8 (47.1)                                      | 121 (46.2)                                                    | 1.04 (0.39–2.77)                           | 1.12 (0.40–3.15) | 0.170 |                      |
| Weight at delivery (g)                        |                                                               |                                             |             |   |                      |
| 3460 (3109–3810)                              | 3475 (3198–3859)                                              | 0.733                                       |             |   |                      |
| Apgar at 5 min                                |                                                               |                                             |             |   |                      |
| <7                                             | 0 (0)                                                         | 0 (0)                                       | NR          | NR |                      |
| Unknown                                       | 0 (0.0)                                                       | 3 (1.1)                                     |             |   |                      |
| Median                                         | 10 (10–10)                                                    | 10 (10–10)                                  | 0.170       |     |                      |
| Umbilical cord pH (arterial)                  |                                                               |                                             |             |   |                      |
| <7.10                                          | 0 (0.0)                                                       | 8 (3.7)                                     | NR          | NR |                      |

(Continues)
In this prospective population-based cohort study, we found 418 validated cases of SARS-CoV-2 among pregnant women, corresponding to an incidence of 5.1 per 1000 pregnancies. Only 23 women (5.5%) required hospital admission due to the COVID-19 infection. Risk factors for infection were asthma and being foreign born, whereas obesity, smoking, infection after GA 22 weeks, and asthma increased the risk of hospital admission due to COVID-19. We found an increased risk of late termination of pregnancy, but no difference in any delivery or neonatal outcomes among infected women or women with severe infection.

Minority ethnicity has been identified as a risk factor for SARS-CoV-2 infection in both pregnant and non-pregnant women.2–5,8 The increased risk level found among foreign-born women in this study is similar to that reported in a large systematic review for women of minority ethnicity.2

The etiology of the disparity is not clear, but it is probably multifaceted and related to cultural and socio-economic factors rather than to SARS-CoV-2.

The identified risk factors for severe infection comprising asthma, obesity, and GA at the time of infection are similar to risk factors identified in previous studies.2,3 Smoking in pregnancy has not been described previously, but seems a plausible risk factor because of its effect on lung tissue, and smoking women might sooner develop severe respiratory symptoms requiring hospital care. Previous population-based studies have primarily included women admitted to hospital,3,7,8 and our results in the more severe cases (Table 3) are therefore comparable to the results of these studies.

Women becoming infected after GA 22 weeks had a higher risk of COVID-19-related hospital admission than women becoming infected before 22 weeks. This might indicate an increasing severity of disease with higher GA at infection. However, it may also be explained by a lower threshold to admit women with disease in late pregnancy.

Women with SARS-CoV-2 infection had, as expected, a much higher risk of pneumonia, but otherwise we found no increased risk for adverse maternal or neonatal outcomes in infected compared with non-infected pregnant women. Previous studies have found increased risks of admission to an ICU, induction of labor, preterm delivery, and admission to a NICU,2–6,20,21 which we could not confirm. The lack of association in our study might be related to the fact that we included all cases of SARS-CoV-2 infection in pregnancy independent of severity. The previously shown associations between SARS-CoV-2 and severe outcomes might be related to severity of disease. We found no statistically significant differences in outcomes among cases requiring hospital admission for COVID-19 compared with less severe cases, but relatively high-risk differences for cesarean section, induction of labor, and admission to a NICU of the neonate. The lack of statistical associations is likely due to low numbers. In a Nordic collaborative study, women with severe COVID-19 were at increased risk of induction of labor cesarean delivery, and preterm delivery.22 We found few cases of early pregnancy complications among the SARS-CoV-2-infected women. However, after adjustment for exposure time, the risk of termination of pregnancy was higher among the SARS-CoV-2-infected women. In Denmark, all women admitted to hospital are tested for SARS-CoV-2, and we assume that the increased rate of terminations is partly related to more
frequent testing and consequently a higher detection rate of SARS-CoV-2 among women opting for provoked abortion rather than the SARS-CoV-2 diagnosis itself.

This study has several strengths. The major strength is the combination of real-time register-based data considered complete and prospectively collected medical record data, allowing for validation, analysis of disease severity, and multivariate analyses. Furthermore, the comparison population comprised all pregnancies from the same inclusion period as the SARS-CoV-2 cases, thereby adjusting for the possible consequences of community regulations during a pandemic. Additionally, we identified the vast majority of SARS-CoV-2 cases in pregnancy because testing was widespread in Denmark during the inclusion period, and the DCOD data were validated against registry data.

The study also has limitations. First, the register data set was pseudoanonymized, making individual-level linkage to DCOD impossible. Additionally, the data sources of the DCOD and the national registers are different, and the data might not be directly comparable. Nevertheless, the number of SARS-CoV-19 cases was similar in the two cohorts, and data did not differ significantly between the cohorts, indicating agreement between cases and data sources. Some descriptive variables, including BMI and smoking status, are not reported to the registers before delivery and are not reported for early pregnancy losses, causing higher rates of missing data in the registers. Nevertheless, the rates of missing data were similar in the infected and non-infected groups, reducing the risk of bias caused by the missing numbers. Additionally, complete data were available in the DCOD, which also allowed for national surveillance of the infection to support national guidelines until register data were available. Second, the lack of association in some outcomes for severe cases might be a result of low numbers. Additionally, the threshold of admitting pregnant women to hospital due to COVID-19 symptoms might be lower than for non-pregnant women, thus diluting the risk estimates of severe disease. Third, universal testing of pregnant women was not implemented in Denmark before May 2020, and we might therefore have missed SARS-CoV-2-positive cases early in the inclusion period. Furthermore, MiBa only included information on PCR tests, so we might have missed pregnant women diagnosed through antigen or antibody tests, which were possibly milder cases. Inclusion of these plausibly positive but non-identified cases in the comparison population of pregnancies might have affected our estimates.

5 | CONCLUSION

In this prospective population-based cohort study with universal SARS-CoV-2 testing, we found no difference in outcomes related to delivery or the neonate among infected women compared with non-infected women. Nor did severity of infection statistically affect the results, but these results have to be interpreted with caution because of low numbers. The results indicate that the outcomes of SARS-CoV-2 infection in pregnancy might not be as severe as proposed by previous studies. The testing strategy and how cases are included naturally influences the results and should be considered.

We found that the incidence of termination of pregnancy among SARS-CoV-2-infected women was increased compared with that in non-infected pregnant women, which might be related to universal screening of women admitted to hospital. Further studies are needed to explore a possible relation between late termination of pregnancy and SARS-CoV-2 infection.

ACKNOWLEDGEMENTS

The authors would like to thank EasyTrial, who provided their clinical trial management software, used for data management in the DCOD study, free of charge for this study because the company offered free access to the software to COVID-19 research projects. The authors also wish to thank Professor Marian Knight, DPhil, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK, for her initiation of the International Network of Obstetric Survey Systems study, in which the DCOD participates, and her contribution to the international case report form, on which the DCOD is based.

CONFLICT OF INTERESTS

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AA, LK, MB, LS, KHR, JJ, and LP conceived the registry study, and AA and LK conceived the DCOD study. AA, LK, and MB designed and planned the combined study. AA, MB, TP, and FP acquired and analyzed the data for the cohort study. KW, MI, FJ, ER, CA, IS, TC, JM, LB, BL, AT, MK, BH, LJ, SS, LS, KK, MP, ÅK, MV, DT, MT, LA, AB, AG, CBA, RF, LH, LHv, AS, SR, AA, and LK acquired and managed the DCOD data set and AA analyzed the DCOD data. AA wrote the first draft of the manuscript; MB, LK, TP, LS, KHR, and JJ revised the manuscript critically; and all authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Aabakke AJM, Krebs L, Petersen TG, et al. SARS-CoV-2 infection in pregnancy in Denmark—characteristics and outcomes after confirmed infection in pregnancy: A nationwide, prospective, population-based cohort study. Acta Obstet Gynecol Scand. 2021;100:2097-2110. https://doi.org/10.1111/aogs.14252