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ORIGINAL RESEARCH ARTICLE

Risk factors for and pregnancy outcomes after SARS-CoV-2 in pregnancy according to disease severity: A nationwide cohort study with validation of the SARS-CoV-2 diagnosis

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Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease; DCOD, the Danish COVID-19 in pregnancy database; DNPR, The Danish National Patient Register; GA, gestational age in completed weeks; HR, hazard ratio; MiBa, Danish Microbiology Database; OR, crude odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age.

Anna J. M. Aabakke and Tanja G. Petersen: shared first authorship.

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Abstract

Introduction: We identified risk factors and outcomes associated with SARS-CoV-2 infection in pregnancy in a universally tested population according to disease severity and validated information on SARS-CoV-2 during pregnancy in national health registers in Denmark.

Material and methods: Cohort study using data from national registers and medical records including all pregnancies between March 1, 2020 and February 28, 2021. We compared women with a validated positive SARS-CoV-2 test during pregnancy with non-infected pregnant women. Risk factors and pregnancy outcomes were assessed by Poisson and Cox regression models and stratified according to disease severity defined by hospital admission status and admission reason (COVID-19 symptoms or other). Using medical record data on actual period of pregnancy, we calculated predictive values of the SARS-CoV-2 diagnosis in pregnancy in the registers.

Results: SARS-CoV-2 infection was detected in 1819 (1.6%) of 111 185 pregnancies. Asthma was associated with infection (relative risk [RR] 1.63, 95% confidence interval [CI] 1.28–2.07). Risk factors for severe COVID-19 disease requiring hospital admission were high body mass index (median ratio 1.06, 95% CI 1.04–1.09), asthma (RR 7.47, 95% CI 3.51–15.90) and gestational age at the time of infection (gestational age 28–36 vs <22: RR 3.53, 95% CI 1.75–7.10). SARS-CoV-2-infected women more frequently had hypertensive disorders in pregnancy (adjusted hazard ratio [aHR] 1.31, 95% CI 1.04–1.64), early pregnancy loss (aHR 1.37, 95% CI 1.00–1.88), preterm delivery before gestational age 28 (aHR 2.31, 95% CI 1.01–5.26), iatrogenically preterm delivery before gestational age 37 (aHR 1.49, 95% CI 1.01–2.19) and small-for-gestational age children (aHR 1.28, 95% CI 1.05–1.54). The associations were stronger among women admitted to hospital for any reason. The validity of the SARS-CoV-2 diagnosis in relation to pregnancy in the registers compared with medical records showed a negative predictive value of 99.9 (95% CI 99.9–100.0) and a positive predictive value of 82.1 (95% CI 80.4–83.7).

Conclusions: Women infected with SARS-CoV-2 during pregnancy were at increased risk of hypertensive disorders in pregnancy, early pregnancy loss, preterm delivery and having children small for gestational age. The validity of Danish national registers was acceptable for identification of SARS-CoV-2 infection during pregnancy.

KEYWORDS

cohort studies, COVID-19, obstetric delivery, pregnancy complications, pregnancy outcome, prospective studies, severe acute respiratory syndrome coronavirus 2, validation study

1 | INTRODUCTION

The consequences of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy have been studied intensively. Risk factors for developing severe coronavirus disease (COVID-19) include increasing maternal age and body mass index (BMI), minority ethnicity, comorbidities and infection in late pregnancy.^{1,2} SARS-CoV-2 infection is associated with preterm delivery, preeclampsia, cesarean delivery and stillbirth.¹ However, risk estimates vary according to country, testing strategy, population and comparison group and, more recently, virus variant and vaccination status.^{1,3-5} Overall, the reported risk estimates seem smaller in the Scandinavian population than in other countries.⁶ A Danish study, including 418 pregnant women infected during the first 8 months of the pandemic, found few associated risk factors and complications, possibly due to low numbers.⁷ Later, the infection rate increased noticeably, urging an updated analysis.

The Nordic countries have well-established and validated registers.⁸⁻¹⁰ However, the SARS-CoV-2 diagnosis in relation to pregnancy has not previously been validated by combining register data with information from medical records.

The objective of this study was to expand prior research on risk factors for and outcomes after SARS-CoV-2 infection in pregnancy in a universally tested unvaccinated population and to investigate the influence of admission to hospital during infection on the severity of pregnancy outcomes. Additionally, we aimed to validate information on SARS-CoV-2 infection during pregnancy in national registers using medical records as reference standard.

2 | MATERIAL AND METHODS

This was a national cohort study investigating the association between SARS-CoV-2 infection in pregnancy and maternal characteristics and pregnancy outcomes according to status on admission to hospital using national registers and information from medical records in Denmark. This study updated published data from the first 8 months of the pandemic.⁷

The study used register data obtained from the Danish National Patient Register (DNPR),⁸ Danish Microbiology Database (MiBa),¹¹ the Civil Registration System^{12,13} and data from medical records registered in the Danish COVID-19 in pregnancy database (DCOD).⁷ MiBa contains information about all SARS-CoV-2 PCR tests and, from December 2020, also antigen tests. Pregnancy and maternity care is free of charge in Denmark, with mandatory reporting to the national registers, and the registers are therefore considered complete. All Danish citizens have a unique personal identification number which allows for linkage between registers.¹⁴

The study population was identified in the DNPR and comprised all women registered with a pregnancy or birth-related ICD10 diagnosis or procedure between March 1, 2020 and February 28, 2021 as specified in Appendix S1. Pregnancies were included from the date of the first day of the last menstrual period, which was

Key message

Women with SARS-CoV-2 infection in pregnancy had an increased risk of hypertensive disorders in pregnancy, early pregnancy loss, preterm delivery and small-for-gestational age. The validity of the SARS-CoV-2 diagnosis in relation to pregnancy in the Danish national registers was acceptable.

calculated based on the registered gestational age (GA) at delivery or abortion (Appendix S1). For deliveries, miscarriages and abortions with a missing registration of GA, GA was imputed based on the mean GA within the categories. Pregnant women identified in the registers were followed until April 21, 2021.

SARS-CoV-2-positive women were identified through the DCOD. DCOD is a database of all women with a positive SARS-CoV-2 test during pregnancy in Denmark between March 1, 2020 and February 28, 2021, with information based on medical records, as previously described.⁷ Eligible SARS-CoV-2 tests in DCOD included PCR tests, antigen tests or detection of antibodies (IgG and total antibodies in serum) combined with a history of COVID-19 symptoms during pregnancy. To secure data completeness in DCOD, cases were validated bimonthly against data obtained from the DNPR and MiBa. Non-reported cases were entered into DCOD retrospectively if the woman was confirmed pregnant at the time of the positive SARS-CoV-2 test.

Exposed pregnancies admitted to hospital with a concurrent SARS-CoV-2 infection, defined as admission and discharge on two different dates and a positive test within 14 days before or during admission, were stratified as pregnancies admitted to hospital for any reason with a concurrent SARS-CoV-2 infection or pregnancies admitted to hospital due to COVID-19 symptoms.

The definition of characteristics and outcomes including the procedure and diagnostic codes used to identify these in the DNPR are available in Appendix S2. Information on characteristics and outcomes was derived from the DNPR for both the infected and the non-infected populations.

2.1 | Statistical analyses

Maternal characteristics according to SARS-CoV-2 and hospital admission status are presented as count and frequency for categorical variables and by median with interquartile range for continuous variables. Risk factors for infection and hospital admission were analyzed using Poisson regression, except for gestational diabetes, which was included as a time-varying variable in a Cox regression model.

All maternal, pregnancy, birth and delivery outcomes except mode of delivery were analyzed using Cox regression models including SARS-CoV-2 as a time-varying variable. Risk time started at the

date of the first pregnancy-related hospital contact, except for the outcomes small for gestational age (SGA), intrauterine fetal death and preterm birth where women entered at GA 22 weeks. Follow-up ended at the date of event or April 21, 2021. Mode of delivery and binary neonatal outcomes were analyzed using Poisson regression. For continuous outcomes, the ratio of the medians was analyzed using linear regression including log-transformed outcome variables to account for non-normal distribution of residuals.

Estimates are presented as relative risks (RR) for the Poisson regressions and hazard ratios (HR) for the Cox regressions, with 95% confidence intervals (CI) obtained using clustered sandwich estimators to adjust for the dependency of multiple pregnancies in the same women. For the log-transformed linear regression models, estimates are presented as median ratios with 95% CI obtained by bootstrapping.

The selection of potential confounders was based on previously identified risk factors⁷ and guided by the use of directed acyclic graphs (Figure S1). All multivariate models were adjusted for maternal age, last menstrual period (to consider seasonal variations) and preexisting asthma. Delivery, birth and neonatal outcomes were further adjusted for pre-pregnancy BMI categories, smoking in pregnancy and parity, which are only available in the DNPR for women who have delivered by the end of follow-up. Observations with missing data on these covariates (4.4%) were excluded from the analyses. Possible effect modifications between SARS-CoV-2 infection and covariates were tested by including an interaction term in the regression models, and stratified analyses were performed for possible effect modifiers.

Additionally, we computed the positive and negative predicted values of identifying SARS-CoV-2 correctly during pregnancy in the national registers by comparison with validated data from the DCOD. Several sensitivity analyses were performed:

- Predictive values of the obstetric outcomes early pregnancy loss, termination of pregnancy, and live birth in DNPR compared with DCOD in women with a registered outcome in both the DNPR and DCOD ($n = 1096$).
- Restricted analyses of maternal and pregnancy outcomes for deliveries to allow for adjustment for BMI, smoking and parity.
- Extension of the exposure period to April 21, 2021 by defining SARS-CoV-2 exposure as registered in MiBa during (i) the consecutive 2 months after the inclusion period and (ii) the entire period.
- Assessment of smoking according to DCOD data because information on smoking was missing in the main analyses for women with a miscarriage or abortion or who were still pregnant at the end of the study.

Additional analyses included:

- Analysis of characteristics and outcomes according to time period of infection: March 1 to July 31, 2020 (first wave) and August 1, 2020 to February 28, 2021 (second wave).
- Analysis of risk of SGA and modes of delivery according to GA at time of infection (GA <22, 22–27, 28–36 or ≥37 weeks) and time from infection to outcome (≤14 days or >14 days).

Missing data were excluded from all analyses, and data numbers <5 are not reported to avoid identification.¹⁵ Data were analyzed using STATA/MP16.

2.2 | Ethics statement

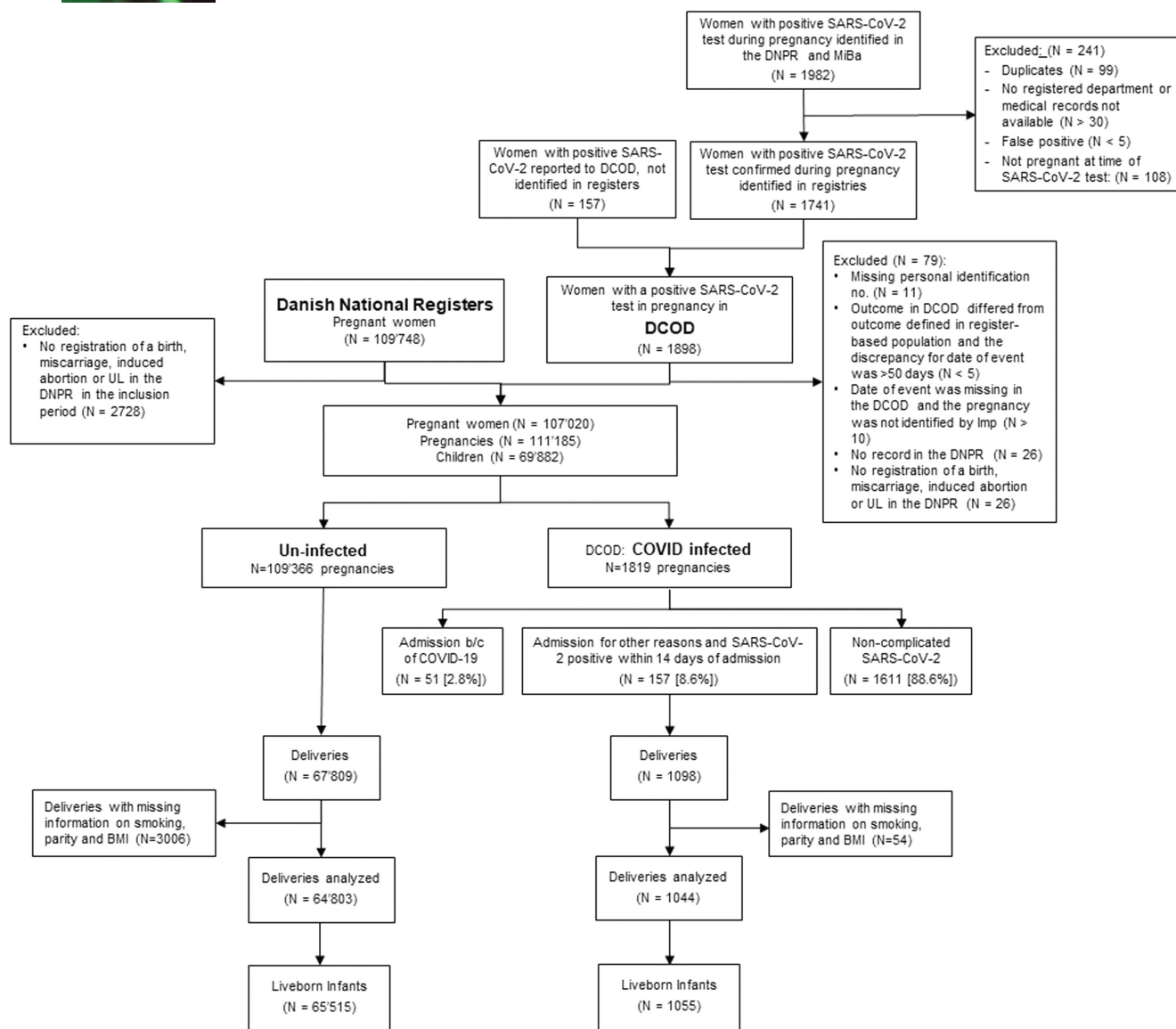
The study was approved by the Danish Patient Safety Authority on April 24, 2020 (reg. no. 31-1521-252), the regional Data Protection Agency in Region Zealand on March 23, 2020 (reg. no. REG-022-2020) and the regional Data Protection Agency in Region of Southern Denmark on April 15, 2020 (reg. no. 20/17416). Individual patient consent was not required. The study is reported according to STROBE guidelines.¹⁶

3 | RESULTS

Among 107 020 women with 111 185 pregnancies between March 1, 2020 and February 28, 2021, SARS-CoV-2 infection was confirmed in 1819 pregnancies, equivalent to an overall cumulative incidence of 1.6%, with the monthly incidence rate ranging from 0.2 per 1000 pregnancies in June to 13.7 in December (Figure S2). In all, 208 (11.4%) of the infected pregnancies were admitted to hospital within 14 days of a positive test, and 51 (2.8%) were admitted because of COVID-19 symptoms (Figure 1).

Women with SARS-CoV-2 infection more frequently had asthma (RR 1.63, 95% CI 1.28–2.07) but less frequently smoked (RR 0.70, 95% CI 0.56–0.87) compared with non-infected women (Table 1). Women admitted to hospital with a concurrent infection independent of admission reason more frequently had asthma (RR 3.12, 95% CI 1.84–5.28) compared with non-infected women (Table S1). Severe COVID-19 causing admission to hospital was associated with high BMI (median ratio 1.06, 95% 1.04–1.09) and preexisting asthma (RR 7.47, 95% CI 3.51–15.90) (Table 1). Smoking was also identified as a risk factor according to DCOD data, (data not presented RR 2.49, 95% CI 1.10–5.63. Missing information: non-infected: 3.8%, admission COVID-19: ($n < 5$)). Extending the exposure period did not change the associations (Table S3).

The outcomes of the SARS-CoV-2-infected pregnancies are presented in Table 2; Table S2. SARS-CoV-2 infection was associated with an increased risk of early pregnancy loss (adjusted hazard ratio [aHR] 1.37 95% CI 1.00–1.88). The overall rate of termination of pregnancy was not increased (aHR 1.15, 95% CI 0.77–1.73); however, in women younger than 25 years, termination of pregnancy was associated with SARS-CoV-2 infection (aHR 2.51, 95% CI 1.21–5.21, data not presented). Infection was associated with an increased risk of hypertensive disorders of pregnancy after infection (aHR 1.31, 95% CI 1.04–1.64), extremely preterm delivery before GA week 28 (aHR 2.31, 95% CI 1.01–5.26) and iatrogenic preterm delivery before GA week 37 (aHR 1.49, 95% CI 1.01–2.19). Children of infected mothers were more often SGA below the 10th percentile (aHR 1.28, 95% CI 1.05–1.54), while the estimate for SGA below the 2.3rd



Inclusion period: 1 March 2020 – 28 February 2021

Follow-up in DNPR until 21 April 2021

DNPR: Danish National Patient Register, DCOD: Danish Covid-19 in pregnancy database

FIGURE 1 Flow through the study.

percentile yielded an aHR of 1.24 (95% CI 0.89–1.72). The risk of SGA was not dependent on GA at time of infection (data not presented). Infected women admitted for any reason had more obstetric complications than non-infected women, including hypertensive disorders of pregnancy (aHR 4.38, 95% CI 2.66–7.21), SGA (<10th percentile: aHR 2.96, 95% CI 1.76–4.97; <2.3rd percentile aHR 2.75, 95% CI 1.21–6.24) and preterm delivery before GA week 37 (aHR 5.16, 95% CI 2.90–9.20), and more frequently had induction of labor (aHR 2.45, 95% CI 1.71–3.52) and were admitted to an intensive care unit (aHR 15.96, 95% CI 6.45–39.48). Admission to hospital due to COVID-19 was non-significantly associated with induction of labor (aHR 1.65, 95% CI 0.82–3.31), cesarean delivery (aHR 1.50, 95% CI

0.98–2.30) and admission to neonatal intensive care unit (aHR 1.66, 95% CI 0.94–2.92). Associations did not change when extending the exposure period (Table S4), nor did the association with hypertensive disorders of pregnancy in a sub-analysis of births including adjustment for BMI, parity and smoking (data not presented).

Table 3 presents the SARS-CoV-2 characteristics. The risk of admission to hospital due to COVID-19 symptoms increased with higher GA at time of infection, and women admitted due to symptoms were at increased risk of being delivered within 14 days of infection compared with infected non-admitted women.

The validity of the SARS-CoV-2 diagnosis in pregnancy in the national registers compared with the DCOD is presented in Table 4.

TABLE 1 Risk factors for SARS-CoV-2 infection in pregnant women overall, and if admitted to hospital because of COVID-19 compared with non-infected women in Denmark between March 2020 and February 2021

	Non-infected pregnancies	SARS-CoV-2 infected pregnancies		SARS-CoV-2 infected pregnancies	
			Admission COVID-19 ^a		Admission COVID-19 ^a
		All infected		All infected	
	<i>n</i> = 109 366	<i>n</i> = 1819	<i>n</i> = 51	RR/MR (95% CI)	RR/MR (95% CI)
Maternal characteristics					
Age, years					
<25	13 721 (12.55)	222 (12.2)	6 (11.8)	1 (ref.)	1 (ref.)
25–34	75 854 (69.36)	1309 (72.0)	34 (66.7)	1.07 (0.93;1.23)	1.03 (0.43;2.44)
≥35	19 791 (18.10)	288 (15.8)	11 (21.6)	0.90 (0.76;1.07)	1.27 (0.47;3.44)
Median	30.0 (27.0–33.0)	29.0 (26.0–33.0)	29.0 (27.0–34.0)	0.99 (0.98;1.00)	1.02 (0.97;1.08)
BMI, kg/m ²					
<25	51 524 (58.2)	979 (57.8)	22 (45.8)	1 (ref.)	1 (ref.)
25–29.9	22 777 (25.8)	437 (25.8)	10 (20.8)	1.01 (0.90;1.13)	1.03 (0.49;2.17)
30–34.9	8845 (10.0)	179 (10.6)	11 (22.9)	1.06 (0.91;1.25)	2.91 (1.41;6.00)
>35	5259 (6.0)	100 (5.9)	5 (10.4)	1.00 (0.82;1.23)	2.23 (0.84;5.87)
Missing	20 961 (19.2)	124 (6.8)	13 (25.5)		
Median	24.0 (21.0–27.0)	24.0 (21.0–27.0)	26.0 (23.0–31.5)	1.00 (1.00;1.01)	1.06 (1.04;1.09)
Smoking					
	6560 (7.6)	89 (5.4)	<5	0.70 (0.56;0.87)	NA
Missing	22 536 (20.6)	170 (9.4)	13 (25.5)		
Preexisting asthma	2658 (2.4)	71 (3.9)	8 (15.7)	1.63 (1.28;2.07)	7.47 (3.51;15.90)
Preexisting hypertension	969 (0.9)	17 (0.9)	<5	1.06 (0.65;1.71)	NA
Preexisting diabetes	652 (0.6)	12 (0.7)	0 (0.0)	1.11 (0.62;1.96)	NR
Pregnancy characteristics					
Parity					
Multiparous	51 706 (55.4)	949 (54.2)	33 (64.7)	0.95 (0.87;1.05)	1.48 (0.83;2.62)
Missing	16 045 (14.7)	69 (3.8)	<5		
Multiple pregnancy					
Multiples	1334 (1.2)	26 (1.4)	0 (0.0)	1.17 (0.79;1.74)	NR
				HR (95% CI)	HR (95% CI)
Gestational diabetes ^b	4558 (4.2)	34 (2.2)	<5	1.03 (0.73;1.45)	NA

Note: Data are presented as count (%) or median (interquartile range). Relative risks are calculated using Poisson regression. Hazard ratios are calculated using Cox regression including the pregnancy characteristics as time-varying variables. Ratios of the medians are calculated using linear regression analyses including log-transformed outcome. The confidence interval indicates that the bold values are significant.

Abbreviations: BMI, body mass index; CI, confidence interval; GA, gestational age; HR, hazard ratio; MR, median ratio; NR, not relevant; NA, not available; RR, relative risk.

^aAdmission to hospital because of COVID-19 was defined as admission and discharge on two different dates because of COVID-19 symptoms and a positive test within 14 days before or during admission.

^bGestational diabetes is only counted as occurring among the infected pregnancies if it occurs before infection, and women with infection before first pregnancy-related hospital contact are censored. Thus, the percentages might differ in relation to the total number of infected women noted in the table.

The positive predictive value of identifying a positive SARS-CoV-2 test correctly during pregnancy was 82.1 (95% CI 80.4–83.7) and the negative predictive value was 99.9 (95% CI 99.9–100.0).

Differences in characteristics and outcomes between the first and second waves of the COVID pandemic in Denmark are presented in Table S5. Disregarding wave length, which varied by

TABLE 2 Maternal, pregnancy, delivery and neonatal outcomes after SARS-CoV-2 infection in pregnancy overall and in women admitted to hospital because of COVID-19 compared with non-infected pregnancies in Denmark between March 2020 and February 2021

		SARS-CoV-2-infection during pregnancy		SARS-CoV-2-infection during pregnancy		SARS-CoV-2-infection during pregnancy	
		No infection in pregnancy		All infected	Admission COVID-19 ^a	All infected	Admission COVID-19 ^a
Maternal and pregnancy outcomes	Pregnancies	n = 109 366	n = 1819	n = 51		HR (95% CI)	aHR (95% CI)
Pregnancy-related hypertensive disorder ^b		3663 (3.4)	78 (4.3)	<5		1.40 (1.12;1.75)	1.31 (1.04;1.64)
Admission to ICU ^b		363 (0.3)	8 (0.4)	<5		1.44 (0.71;2.90)	1.46 (0.72;2.97)
Death		0 (0.0)	0 (0.0)	0 (0.0)		NR	NR
Early pregnancy loss (GA <22 weeks)	All	10 372 (9.5)	48 (2.6)	<5		1.23 (0.89;1.70)	1.37 (1.00;1.88)
	GA <12	8968 (8.2)	39 (2.1)	0 (0.0)		1.23 (0.86;1.76)	1.33 (0.93;1.91)
	GA 12-21	1404 (1.3)	9 (0.5)	<5		1.25 (0.65;2.43)	1.59 (0.82;3.09)
Termination of pregnancy (GA <22 weeks)	All	8152 (7.5)	35 (1.9)	<5		1.21 (0.81;1.81)	1.15 (0.77;1.73)
	GA <12	7641 (7.0)	29 (1.6)	<5		1.14 (0.73;1.77)	1.08 (0.69;1.70)
	GA 12-21	511 (0.5)	6 (0.3)	0 (0.0)		1.74 (0.78;3.91)	1.72 (0.76;3.89)
Delivery outcomes	Deliveries	n = 64 803	n = 1044	n = 40		HR/MR (95% CI)	aHR/aMR (95% CI)
GA at delivery, weeks	Median	40+1 (39+0 to 41+0)	40+0 (39+0 to 40+6)	39+4 (38+2 to 40+4)		1.00 (0.99;1.00)	1.00 (1.00;1.01)
Preterm birth <GA 37 weeks		3487 (5.4)	66 (6.3)	<5		1.51 (1.18;1.93)	1.26 (0.99;1.62)
	Iatrogenic	1167 (1.8)	27 (2.6)	<5		1.84 (1.25;2.69)	1.49 (1.01;2.19)
	Spontaneous	2320 (3.6)	39 (3.7)	<5		1.35 (0.98;1.85)	1.14 (0.83;1.57)
Preterm birth <GA 28 weeks		238 (0.4)	6 (0.6)	<5		3.91 (1.73;8.81)	2.31 (1.01;5.26)
Induction		14 526 (22.4)	227 (21.7)	9 (22.5)		1.04 (0.91;1.19)	1.01 (0.89;1.16)
	Vaginal	52 113 (80.4)	818 (78.4)	27 (67.5)		RR (95% CI)	aRR (95% CI)
	Operative vaginal delivery	3580 (5.5)	61 (5.8)	0 (0.0)		0.97 (0.94;1.01)	0.99 (0.95;1.02)
						1.06 (0.83;1.35)	1.11 (0.87;1.42)
Cesarean delivery (CD)		12 492 (19.3)	222 (21.3)	13 (32.5)		1.10 (0.98;1.24)	1.69 (1.08;2.64)
						1.05 (0.94;1.19)	1.50 (0.98;2.30)

TABLE 2 (Continued)

		SARS-CoV-2-infection during pregnancy		SARS-CoV-2-infection during pregnancy	
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Note: Data are presented as count (%) or median (interquartile range). Relative risks are calculated using Poisson regression. Hazard ratios are calculated using Cox regression including the pregnancy characteristics as time-varying variables. Ratios of the medians are calculated using linear regression analyses including log-transformed outcome. All outcomes were adjusted for maternal age, the date of the first day of the last menstrual period and preexisting asthma. Delivery, birth and neonatal outcomes were additionally adjusted for pre-pregnancy BMI, smoking and parity, and observations with missing data on these covariates (4.4%) were excluded from the analyses. The confidence interval indicates that the bold values are significant.

Abbreviations: CD Cesarean delivery; CI, confidence interval; GA, gestational age; HR, hazard ratio; ICU, Intensive care unit; MR, median ratio; NR, not relevant; NA, not available; RR, relative risk.

^aAdmission to hospital because of COVID-19 was defined as admission and discharge on two different dates because of COVID-19 symptoms and a positive test within 14 days before or during admission.

^bFor the outcomes pregnancy-related hypertensive disorder and admission to ICU, the event is only counted as occurring among the infected pregnancies if it occurs after the date of infection, and women with the outcome before the first pregnancy-related hospital contact are censored. Thus, the percentages might differ in relation to the total number of infected pregnancies noted in the table.

2 months, there were fewer infections during the first wave ($n = 156$ vs 1663). During the second wave, relatively fewer women among the SARS-CoV-2 infected had asthma (crude odds ratio [OR] 0.27, 95% CI 0.15–0.49) and relatively more women were diagnosed later in pregnancy compared with during the first wave.

The validity analyses of selected pregnancy outcomes are presented in Table S6. The positive predictive value was high for births (99.9, 95% CI 99.5–100.0) and termination of pregnancy (100.0, 95% CI 89.4–100.0) but lower for early pregnancy loss (82.9, 95% CI 67.9–92.9).

4 | DISCUSSION

In this population-based study of SARS-CoV-2 infection in pregnancy, we found asthma associated with infection during pregnancy. Risk factors for developing severe disease requiring admission to hospital were smoking, asthma and high BMI. Infected women were, independent of disease severity, at increased risk of hypertensive disorders of pregnancy, early pregnancy loss, preterm delivery and delivering SGA children. The risk of admission because of COVID-19 symptoms increased with increasing GA at time of infection. The Danish national health registers were found to have an acceptable validity for identification of women with SARS-CoV-2 during pregnancy.

Our results are similar to findings from previous studies except that we did not find an association with age.^{1,2} For several outcomes, the absolute risks in our population were lower than in studies from other countries and the increases in absolute risks were generally small.^{1,2} The reason for this could be that the Danish pregnant population is overall low-risk and there is free access to public healthcare in Denmark.

We found that women admitted with a concurrent SARS-CoV-2 infection had higher risks of several adverse obstetric outcomes. However, women admitted during pregnancy represent high-risk pregnancies with higher risks of severe outcomes than non-admitted women – independent of infection status. When only women admitted to hospital are included in SARS-CoV-2 studies, risk estimates are likely to be higher due to the exclusion of infected non-hospitalized individuals and this has to be considered in the interpretation of results of SARS-CoV-2 in pregnancy studies.

We found an increased occurrence of hypertensive disorders of pregnancy after SARS-CoV-2 infection, which has also been described previously and at similar rates.^{17,18} SARS-CoV-2 infection has been associated with increased levels of transaminases and thrombocytopenia,^{19–21} and the infection may mimic the symptoms of preeclampsia, making differential diagnosing difficult. Additionally, SARS-CoV-2 infection is associated with an increased risk of thromboembolism, and in rare cases a placental affection by the virus has been observed.^{22–24} We observed an increased rate of SGA after infection, which might be a result of a vascular effect of the virus on the placenta, and this in turn could also explain an association with hypertensive diseases. Additionally, the increased risk of iatrogenic

preterm delivery among infected pregnancies supports the theory of a placental affection compromising the well-being of the baby, leading to emergency delivery.

This study updates previously published results.⁷ There is an 8-month overlap between the two studies comprising 418 SARS-CoV-2-infected pregnant women, which account for less than a quarter of the total study population. This study confirmed the risk factors found in the first study but also identified a number of complications not shown previously possibly due to low numbers. Additionally, in this study we were able to merge data from national registers and DCOD, allowing for more robust analyses and validation of register data.

In contrast to our first study,⁷ we found no overall association between infection and termination of pregnancy. We assume that the association in the first study and in women under 25 years of age in this study was driven by mandatory testing of women admitted to hospital in a population less frequently tested outside a hospital setting.

In Denmark, the testing strategy rapidly intensified during the first months of the pandemic. The differences observed in prevalence, incidence of asthma and GA at time of infection between the first and second waves of the pandemic are probably a consequence of differing testing strategies during the two time periods.

We found an acceptable degree of agreement in the definition of SARS-CoV-2 during pregnancy between the Danish registers and the DCOD, which is based on medical record information. Defining SARS-CoV-2 infection in pregnancy based on information from the Danish Registers can therefore be considered valid. For pregnancy outcomes the positive predictive value of births and termination of pregnancy was very high, indicating high validity, whereas it was lower for early pregnancy loss.

This study has several strengths. First, the study was population-based and comprised large numbers. We were able to merge DCOD data with national register data, allowing for validation, analysis of disease severity and multivariate analyses. Secondly, results were analyzed using survival analyses; thus, time-varying exposures were considered. Thirdly, the comparison population comprised all pregnancies from the same inclusion period as the SARS-CoV-2 cases, thereby adjusting for possible consequences of community regulations during the pandemic. Lastly, a number of sensitivity analyses were performed confirming the robustness of our results.

The study also has limitations. First, we performed a large number of analyses to explore the effect of SARS-CoV-2 infection on pregnancy, which might have resulted in random statistically significant results caused by multiple testing. Secondly, we did not have information on ethnicity or country of birth, which have been associated with disease and disease severity.^{1,7} Thirdly, some descriptive variables including BMI and smoking status are not reported to the registers before delivery and are not available for early pregnancy complications, causing high rates of missing values which might cause bias in the identification of risk factors. However, we were able to compensate for this by using information on smoking from

TABLE 3 Timing of SARS-CoV-2 infection and risk of admission to hospital because of SARS-CoV-2 infection in Denmark between March 2020 and February 2021

SARS-CoV-2 characteristics	SARS-CoV-2-infected pregnancies					
	All infected <i>n</i> = 1819	No admission <i>n</i> = 1611	Admission for any reason ^a <i>n</i> = 208	Admission for COVID-19 ^a <i>n</i> = 51	Admission for any reason ^a RR (95% CI)	Admission COVID-19 ^a RR (95% CI)
GA, weeks at infection ^b						
<22	853 (46.9)	832 (51.6)	21 (10.1)	12 (23.5)	1 (ref.)	1 (ref.)
22–27	354 (19.5)	334 (20.7)	20 (9.6)	> 15	2.29 (1.26–4.18)	3.22 (1.54;6.73)
28–36	445 (24.5)	398 (24.7)	47 (22.6)	> 20	4.29 (2.60–7.09)	3.53 (1.75;7.10)
≥37	167 (9.2)	47 (2.9)	120 (57.7)	< 5	29.19 (18.93–45.01)	NA
Median	22+6 (14+6 to 31+0)					
Interval infection and delivery						
>14 days		949 (96.4)	47 (24.0)	37 (88.1)	1 (ref.)	1 (ref.)
≤14 days		36 (3.7)	149 (76.0)	5 (11.9)	17.07 (12.80;22.76)	3.25 (1.35;7.84)
Test type						
PCR or antigen test	1646 (90.5)					
Antibodies	9 (0.5)					
Unknown	164 (9.0)					

Note: Data are presented as count (%) or median (interquartile range). Relative risks are calculated using Poisson regression. The confidence interval indicates that the bold values are significant.

Abbreviations: CI, confidence interval; GA, gestational age; NA, not available; RR, relative risk.

^aAdmission to hospital with a concurrent SARS-CoV-2 infection was defined as admission and discharge on two different dates and a positive test within 14 days before or during admission. Admission for any reason: included women admitted due to COVID-19.

^bGA at infection is defined according to date of first positive test in case of a PCR test or date of symptoms in case of an antibody test.

SARS-CoV-2 diagnosis in pregnancy		DCOD	
		No	Yes
MiBA and DNLB	No	108 984	68
	Yes	382	1751
PPV 82.09, 95% CI 80.40–83.70			
NPV 99.94, 95% CI 99.92–99.95			

Abbreviations: DCOD Danish Covid-19 in Pregnancy database—database based on pregnancy information from medical records; PPV, positive predictive value; DNLB, Danish National Patient Register; MiBA, Danish Microbiology Database; NPV, negative predictive value.

the DCOD. Additionally, for women who had delivered, the rate of missing data was reduced and in the adjusted analyses observations with missing data (4.4%) were excluded from the analyses. Finally, universal testing of pregnant women at delivery was not implemented in Denmark before May 2020, and we might therefore have missed SARS-CoV-2-positive cases early in the inclusion period. However, any potential misclassification of exposure would be non-differential and have introduced bias toward the null. From very early in the pandemic, testing in Denmark was widespread and easily accessible, and the DCOD was regularly validated against register data. We therefore assume that we identified the vast majority of infected pregnancies. Last, this study only included cases from the first year of the pandemic, before the implementation of vaccination and influence of new virus variants, which might affect outcomes.^{4,25}

5 | CONCLUSION

Women infected with SARS-CoV-2 during pregnancy had an increased risk of hypertensive disorders of pregnancy, early pregnancy loss, preterm delivery and having children small for gestational age. Danish register data on SARS-CoV-2 infection in pregnancy have an acceptable validity.

AUTHOR CONTRIBUTIONS

AA, TP, LK and MB conceived the registry study, and AA and LK conceived the DCOD study. AA, TP, LK and MB designed and planned the combined study. MB, TP, KR and LP acquired and analyzed the register data. KW, MI, FJ, ER, CA, AL, TC, JM, LB, RZ, BL, AT, MK, BH, LJ, LA, KK, MP, GC, MV, DT, AF, JJ, DM, GD, CBA, RF, LH, LHV, AS, SR, AA and LK acquired, validated and managed the DCOD dataset. AA quality-controlled the DCOD data. AA and TP wrote the first draft of the paper, MB, JJ and LK revised the paper critically, and all authors approved the final version of the paper. All authors accept responsibility for the paper.

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TABLE 4 Agreement between the Danish COVID-19 in pregnancy database (DCOD) and the Danish registers on the diagnosis of SARS-CoV-2 in pregnancy

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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