IMPACT OF SARS-CoV-2 INFECTION ON PREGNANCY OUTCOMES: A POPULATION-BASED STUDY

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SUMMARY

In a large population based-study, the overall rate of pregnancy complications in all women with SARS-CoV-2 infection (symptomatic or asymptomatic) was similar to non-infected women. However, symptomatic COVID-19 was associated with modest increases in preterm delivery and intrapartum fetal distress.

ABSTRACT

Background: A population-based study to describe the impact of SARS-CoV-2 infection on pregnancy outcomes.

Methods: Prospective, population-based study including pregnant women consecutively attended at first/second trimester or at delivery at three hospitals in Barcelona, Spain. SARS-CoV-2 antibodies (IgG and IgM/IgA) were measured in all participants and nasopharyngeal RT-PCR was performed at delivery. The primary outcome was a composite of pregnancy complications in SARS-CoV-2 positive *versus* negative women: miscarriage, preeclampsia, preterm delivery, perinatal death, small-for-gestational age, neonatal admission. Secondary outcomes were components of the primary outcome plus abnormal fetal growth, malformation, intrapartum fetal distress. Outcomes were also compared between positive symptomatic and positive asymptomatic SARS-CoV-2 women.

Results: Of 2,225 pregnant women, 317 (14.2%) were positive for SARS-CoV-2 antibodies (n=314, 99.1%) and/or RT-PCR (n=36, 11.4%). Among positive women, 217 (68.5%) were asymptomatic, 93 (29.3%) had mild COVID-19 and 7 (2.2%) pneumonia, of which 3 required intensive care unit admission. In women with and without SARS-CoV-2 infection, the primary outcome occurred in 43 (13.6%) and 268 (14%), respectively [risk difference -0.4%, (95% CI: -4.1% to 4.1)]. As compared with non-infected women, women with symptomatic COVID-19 had increased rates of preterm delivery (7.2% *vs.* 16.9%, p=0.003) and intrapartum fetal distress (9.1% *vs.* 19.2%, p=0.004), while asymptomatic women had similar rates to non-infected cases. Among 143 fetuses from infected mothers, none had anti-SARS-CoV-2 IgM/IgA in cord blood.

Conclusions: The overall rate of pregnancy complications in women with SARS-CoV-2 infection was similar to non-infected women. However, symptomatic COVID-19 was associated with modest increases in preterm delivery and intrapartum fetal distress.

Keywords: SARS-CoV-2; COVID-19; Pregnancy; Population-based study.

INTRODUCTION

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease (COVID-19) in pregnancy and their consequences on perinatal outcomes are yet to be fully determined. Data from population-based prospective studies and case series suggest that the infection in pregnancy is mostly asymptomatic or mild,[1–3] but serious illness may develop in a small proportion of women.[4–7]

There is scarce evidence on the impact of SARS-CoV-2 on perinatal outcomes. The reported rates of premature delivery in case series of symptomatic COVID-19 in pregnancy ranged 6-32%.[5–8] While it is anticipated that severe COVID-19 will carry poorer pregnancy outcome,[9] the effect of milder or asymptomatic infections has not been documented. Likewise, most information comes from cases of SARS-CoV-2 reported in the third trimester, but it is unknown whether infection in early pregnancy is associated with increased rates of miscarriage or fetal defects.

We here report a population-based prospective cohort study including early and late pregnant women from the catchment areas of three hospitals in Barcelona (Spain). We conducted universal screening for SARS-CoV-2 infection and evaluated its impact on pregnancy outcomes.

METHODS

Study design, Population and Ethics

A multicentre prospective population-based cohort study from March 15 to May 31, 2020, in Barcelona, Spain. Eligible women were all pregnant women from the catchment areas of three university hospitals (Hospital Sant Joan de Déu [HSJD], Hospital Clinic Barcelona [HCB], and Hospital de Sant Pau [HSP]) during the recruitment periods. Women referred for a diagnosis of SARS-CoV-2 from outside the catchment areas of the participating centers were not eligible for the study. During the 6-week study period, the catchment areas of these hospitals covered approximately 60% of all deliveries attended in public hospitals in the Health region of Barcelona (https://catsalut.gencat.cat/ca/coneix-catsalut/catsalut-territori/barcelona/). For early pregnancy, all women seen in the outpatient setting and who had a blood sampling for first or second trimester Down's syndrome screening (range 10-16 weeks' gestation) from March 15 to May 31 2020, were asked to participate in the study. In those accepting, a sample of serum remaining from routine blood test was analysed for the study. For late pregnancy, all women attending for delivery from April 15 to May 31, 2020, were asked to participate and, if accepting, maternal blood and fetal cord blood samples were obtained. Nasopharyngeal swabs for real time polymerase chain reaction (RT-PCR) were obtained in all women attending delivery.

The study was approved by the Review Board at each institution and informed consent was obtained in all women. Women with COVID-19 were diagnosed and managed according to standard protocols and guidelines.[10,11] A total of 874 women have previously been reported in a study describing the clinical presentation of SARS-CoV-2 in early and late pregnancy, [1] but the rest of patients, as well as the association with perinatal outcomes of the whole study population, have not been reported elsewhere. The study design contemplated recruiting patients just once, so even if due to the timings of recruitment the risk was almost negligible, all women recruited in the early pregnancy cohort were identified to avoid a double recruitment in the delivery cohort.

Data collection

Pregnancy, delivery and neonatal data were obtained from electronic medical files. For all women hospitalized for COVID-19, medical information, pregnancy, delivery and neonatal data were retrieved from hospital files. COVID-19 symptoms were recorded using the same structured questionnaire for all pregnant women, which included questions about risk factors and about any symptom suggestive of COVID-19 noticed between mid-February 2020 and the time of testing for SARS-CoV-2. This time represented 1.5 to 3 months (average 2.2 months, 10 weeks) depending on the date of recruitment. All women testing positive for SARS-CoV-2 by antibodies or RT-PCR were re-interviewed with the same questionnaire 4-5 weeks after recruitment. Among SARS-CoV-2 infected women, we defined as symptomatic those with at least one of the following symptoms: fever, dry cough, loss of taste or smell, dyspnoea, myalgia, diarrhoea, sore throat and rash on skin or discolouration of fingers/toes.

Sample collection and laboratory procedures

Maternal samples were drawn from peripheral veins in all participants. In addition, cord blood from the umbilical vein after cord clamp at delivery was obtained. Serum was separated by centrifugation at 1500 g for 10 min at 4ºC, and samples were immediately stored at −80ºC until analysed. SARS-CoV-2 IgG and IgM/IgA antibodies were tested in all maternal samples and in cord blood samples from SARS-CoV-2 positive mothers using COVID-19 VIRCLIA® Monotest, Vircell Microbiologist, Granada, Spain. All indeterminate results were re-tested (VITROS® Immunodiagnostic Products Anti-SARS-CoV2 Total Tests, Ortho Clinical Diagnostics, Rochester, NY, USA) and classified as positive or negative. Likewise, all samples that were positive for IgM+IgA but negative for IgG in women reporting no symptoms suggestive of COVID-19 during the 10 weeks prior to testing were re-tested by a quantitative suspension array assay based on the xMAP Luminex technology[12] and classified as positive or negative. A more detailed description of laboratory methods is included in the Supplementary Material. A positive serological result was considered in the presence of any of the following: (1) seropositivity for IgG, (2) seropositivity for IgM+IgA in women with symptomatic COVID-19, (3) seropositivity for IgM and/or IgA confirmed by two tests (Vircell and Luminex). See Supplementary Methods for details.

Nasopharyngeal swab samples for SARS-CoV-2 RNA RT-PCR were collected in women attending for delivery. Samples were collected on Micronics tubes with Zymo DNA/RNA Shield Lysis Buffer. RNA was extracted using the Quick-DNA/RNA Viral MagBead kit (Zymo) and the TECAN Dreamprep robot. Five microliters of RNA solution were added to 15 µl of rRT-PCR master mix (Luna Universal Probe One-Step RT-qPCR Kit; New England Biolabs) and used for amplification of SARS-CoV-2 N1 and N2 regions, as well as the human RNase P gene as control, as described in the CDC-006-00019 CDC/DDID/NCIRD/ Division of Viral Diseases protocol released 3/30/2020. A SARS-CoV-2 positive result was considered if the Ct values for N1, N2 and RNase P were below 40. Samples discordant for N1 and N2 were repeated and samples with a Ct ≥ 40 for RNase P were considered as invalid.

SARS-CoV-2 infection was defined either by a positive serological result or positive RT-PCR in nasopharyngeal swab.

Outcomes

The primary end-point for this study was the occurrence of a pregnancy complication, defined by the presence of miscarriage, preeclampsia, preterm delivery, perinatal death, small-for-gestational age or admission to high-dependency neonatal care. This composite outcome was selected from core outcome sets in the context of maternal infections, as defined by stakeholders, including healthcare professionals, researchers, and patients.

Main secondary outcomes were all the individual outcomes considered for the composite primary outcome, plus abnormal fetal growth or malformation at second trimester scan for early pregnancy, and intrapartum fetal distress requiring emergency delivery for late pregnancy. All other clinical findings were exploratory outcomes.

Sample size

Assuming a prevalence of infection of 15% based on the semi-mechanistic Bayesian hierarchical model,[13] if there is truly no difference between the infected and non-infected women in their risk of pregnancy complications (20% in both groups), then 275 infected are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference towards a higher risk in the infected group of more than 10%. To compensate for lost to follow-up, a sample size of 300 infected and 2,250 non-infected women were finally aimed. This sample size of 300 infected women would allow for comparisons between early and late infections (1:2) to test (alpha-risk of 5%) a relative risk of 2 for late infection compared to early infection (assumed risk of hospital admission of 3%) with a power of 80%.

Statistical analysis

Primary analysis. For the primary outcome (pregnancy complications), the primary analysis was the comparison between SARS-CoV-2 infected and non-infected pregnant women.

Secondary analyses. The primary outcomes were also compared between symptomatic *vs.* asymptomatic SARS-CoV-2 infected pregnant women and also between early *vs.* late pregnancy. The secondary and the exploratory outcomes were compared between SARS-CoV-2 infected and non-infected pregnant women, and between SARS-CoV-2 positive symptomatic *vs.* asymptomatic pregnant women.

The analysis was performed using SPSS v26 (New York, USA) including the use of χ^2 test, Student t-test, Mann Whitney U test or Fisher exact test as appropriate. All reported p-values are 2 sided. Differences were considered significant when $p<0.05$. Data is shown as mean (standard deviation, SD), median (interquartile range, IQR) or number (percentages) as appropriate.

RESULTS

Characteristics of the study population

Figure 1 displays the flowchart diagram of the study population. From the initial 2,502 eligible pregnant women, 277 were excluded due to withdrawn consent, unavailable serum samples or undetermined SARS-CoV-2 laboratory results (Suppl. Table 1), thus leaving a final study population of 2,225 pregnant women. Baseline characteristics of women positive and negative for SARS-CoV-2 were mostly similar (Table 1). Among women with SARS-CoV-2, white ethnicity was less frequent (58.7% *vs.* 65.1%, p=0.027) and past history of asthma was higher (6.9% *vs.* 4.1%, p=0.023).

Prevalence of SARS-CoV-2 infection among study groups

We identified a total of 317 (14.2%) women with evidence of SARS-CoV-2 infection, either by positive antibodies (n=314) and/or PCR (n=36), with a similar prevalence in early (15.3%, 141/921) and late (13.5%, 176/1,304) pregnancy. Baseline characteristics of women positive and negative for SARS-CoV-2 were mostly similar, but in SARS-CoV-2 positive women, White ethnicity (58.7% *vs.* 65.1%, p=0.027) was less affected, whereas history of asthma (6.9% *vs.* 4.1%, p=0.023) was more prevalent (Table 1).

Pregnancy outcomes in women with and without SARS-CoV-2 infection

In women with and without SARS-CoV-2 infection, the primary outcome (pregnancy complication) occurred in 13.6% (43/317) and 14% (268/1,908), respectively [risk difference -0.4%, (95% CI: -4.1%

to 4.1)]) (Figure 2, Table 2). Among secondary outcomes, there was a non-significant trend for increased preterm delivery (11.4% *vs.* 7.2%, p=0.054), and a significant increase in intrapartum fetal distress (14% *vs.* 9.1%, p=0.036) in SARS-CoV-2 positive *vs.* negative pregnancies, respectively. Other secondary or exploratory outcomes were similar among groups.

In a secondary analysis comparing women with asymptomatic and symptomatic COVID-19, the rates of the preterm delivery and intrapartum fetal distress were significantly increased in symptomatic women in comparison with non-infected women, while asymptomatic women had rates similar to non-infected pregnant women (Table 3). The proportion of severe small-for-gestational age newborns was higher in symptomatic compared to asymptomatic COVID-19 women (9.6% *vs.* 1%, p=0.006), whereas the proportion of small-for-gestational age was similar (Table 3).

Cord blood was available for analysis in 143 SARS-CoV-2 positive pregnancies. A total of 61 (42.7%) newborns were seropositive for IgG, but none for IgM or IgA. None of these IgG positive newborns presented any symptoms suspicious of infection during the neonatal period.

Clinical presentation of SARS-CoV-2 infection in pregnancy

The clinical features of SARS-CoV-2 infection among study groups are displayed in Supplementary Table 3. Among women with infection, 217 (68.5%) women reported no symptoms. The rate of symptomatic cases and hospital admission was higher in late pregnancy as compared with early pregnancy (Suppl. Table 4). There were seven (4%) patients with pneumonia in the late pregnancy (Suppl. Table 5), of which three required intensive care unit (ICU) admission during the postpartum. Only one of these three patients necessitated prolongation of mechanical ventilation for 48 hours after caesarean section. All women with pneumonia were discharged well. There were no maternal deaths. The rate of ICU admission among COVID-19 symptomatic third trimester women was 4.2% (3/71), for those presenting symptoms during labour 10.7% (3/28) and for those with pneumonia 42.9% (3/7) (Suppl. Table 4). Further details are given in the Supplementary Material section (Results).

DISCUSSION

The data in this population-based study support that, when the full clinical spectrum of the disease is evaluated, the impact of SARS-CoV-2 infection on pregnancy outcomes is small or negligible. The risk of a pregnancy complication as defined in the study was similar in women with and without SARS-CoV-2 exposed in early or late pregnancy. However, symptomatic COVID-19 women had a modest but significant increase in the risk of preterm delivery and intrapartum fetal distress. The information here provides an overall picture of the impact of SARS-CoV-2 infection in pregnancy. We believe the results are reassuring for pregnant women and are useful for healthcare resource planning and clinical management.

Impact on pregnancy outcomes.

This study reports pregnancy follow-up data of SARS-CoV-2 infection in the first or early second trimester. Among 141 positive cases in early pregnancy, there was no evidence of increased rates of miscarriage, fetal defects or abnormal fetal growth at mid-gestation. Previous reports have reported placental infection with SARS-CoV-2 in a case of miscarriage.[14] Anecdotal evidence of placental infection as potential cause of miscarriage has been reported for many viruses.[15] Our study supports that the risk of miscarriage or fetal defects after SARS-CoV-2 infection is, as with other respiratory viruses, very small.[16] In women with SARS-CoV-2 in late pregnancy, the impact of the infection was small or negligible for the majority of patients. However, our data suggest a difference between asymptomatic and symptomatic infections. The study confirms the findings of case series of women with symptomatic COVID-19, reporting increased preterm delivery[5–8] and fetal intrapartum distress.[17] Intrapartum distress could result from maternal poorer oxygenation and inflammatory response,[18] combined with reduced fetal reserve due to placental insufficiency. We observed increased rates of severe small-for-gestational-age newborns in symptomatic COVID-19 women, which is line with recent studies describing placental invasion and thrombotic events by SARS-CoV-2 in placentas analysed after delivery.[19]

In this study, COVID-19 was not associated with increased postpartum obstetric complications such as haemorrhage or infection, but the three patients admitted to ICU deteriorated in the immediate postpartum. This observation is in line with previous studies reporting increased rates of maternal deterioration after delivery in women with COVID-19,[6,7] particularly after caesarean section.[20] Current guidelines[21] recommend promoting vaginal delivery in women with clinically active COVID-19.[22] In this study, the overall rate of caesarean section was not increased in COVID-19 women, supporting that intention of vaginal delivery under strict maternal and fetal surveillance is a safe strategy.

Vertical transmission.

We did not find evidence of anti-SARS-CoV-2 IgM or IgA in cord blood in any of the 143 fetuses from infected mothers evaluated. The observed 43% of positive IgG is in line with a previous study in cord blood of 31 fetuses from infected mothers.[23] Intrauterine transmission of SARS-CoV-2 is supported by case reports describing the virus in newborns, amniotic fluid and placental[24] or cord blood IgM.[25,26] Our results support that vertical transmission of SARS-CoV-2 is very uncommon.[27]

Seroprevalence and clinical presentation

This study was conducted in areas with a high incidence of SARS-CoV-2 infection. The 14.2% prevalence of SARS-CoV-2 in pregnant women is in line with other seroprevalence studies conducted in Spain.[12,28] Prevalence studies in other heavily affected areas, such as New York City in the USA,

reported rates of 16-20%[2] at the peak of the pandemics. This study was mainly conducted in April and May 2020, while the peak of the pandemic in Spain occurred at the end of March (https://www.who.int/countries/esp/). This may explain the relatively low rate of positive RT-PCR results in women screened at delivery, in relation with a much larger proportion of positive serologic results reflecting past infections. The study illustrates the value of population-based seroprevalence studies to capture the high proportion of asymptomatic or mild infections not tested for RT-PCR.[29] In this study, the correlation between antibodies and PCR in women with paired testing was high.

As previously reported,[1,2] SARS-CoV-2 infection during pregnancy was mostly asymptomatic or mild. Notwithstanding this, in a small proportion of pregnant women SARS-CoV-2 can result in serious illness,[7,30] and case series suggest that this risk could be higher in the third trimester.[23] While not the primary goal of this study, we confirmed our previous observations that SARS-CoV-2 could be associated with higher rates of symptomatic disease and severity in third as compared with first trimester pregnant women.[1] It has been suggested that, as described for other respiratory viruses,[31] the risk of COVID-19 severe complications is increased in pregnancy.[7] While the study was not designed to evaluate this question, our data support previous reports suggesting an increased risk in the postpartum, a notion deserving evaluation in large multicentre studies.[31]

Strengths

Among the strengths of the study, this is the largest population-based study on SARS-CoV-2 in pregnancy which provides information on SARS-CoV-2 in early pregnancy too. We studied a population of pregnant women defined by geographic boundaries, i.e. the catchment areas covered by each maternity, which during the study period represented about 60% of all deliveries attended in public hospitals in Barcelona. Including all pregnant women consecutively attending for routine follow-up or delivery provided the opportunity to report the full spectrum of the infection in comparison with multicenter registries of cases, which by definition are biased towards reporting the most severe end of the clinical spectrum. Additionally, data from pregnancy outcomes were highly reliable since all women were attended within the same hospitals. We established several quality controls for serological testing in addition to a larger breadth and accuracy of antibody response including multiple isotypes (IgG, IgA and IgM) and viral antigens, and could perform also RT-PCR in women at delivery, allowing a comparison with serological results.

Weaknesses

Among the weaknesses, for past infections evaluation of symptoms relied on questionnaires. We reduced the risk of inaccuracies by interviewing twice positive women and we found a strong correlation between reported symptoms and serological results. However, we acknowledge that not having repeated the interview in negative women may have resulted in some degree of ascertainment bias. Some first trimester infections may have occurred before pregnancy, but such cases should be very rare considering that women evaluated became pregnant between mid-

January and early March, when SARS-CoV-2 infection cases were negligible in Spain.[13] For early pregnancy infections, we obtained follow-up data until mid-gestation and this information must be completed in future studies. For early pregnancy, RT-PCR was performed in only a few women with symptoms due to the severe restrictions in RT-PCR availability during the first weeks of the pandemics. Therefore, we may have missed asymptomatic infections that were negative for antibodies but positive for RT-PCR at testing, but such cases should be few considering the 85% agreement between positive PCR and serology in women with paired testing. In addition, the serologic assay here used has a reported 89% sensitivity. This study is unpowered to detect rare complications of COVID-19 in pregnancy. International multicentre registries are established as invaluable tools to describe such uncommon complications. For different reasons, RT-PCR in newborns was seldom performed and we could not evaluate these data. This study was conducted in a high-resource setting and consequently these results should not be extrapolated to medium or low-resource settings.

The data of this population-based study in a heavily affected area, support that for the vast majority of pregnancies SARS-CoV-2 infection has small or negligible consequences. For women with symptomatic SARS-CoV-2 in the third trimester, there were modest but significantly increased risks of preterm delivery and intrapartum distress. Likewise, our findings are in line with previous reports suggesting increased risks of severe COVID-19 in symptomatic women during late pregnancy. Vaginal delivery was achieved in most women with clinically active COVID-19 during labour, supporting the safety of such approach. We believe that these findings provide useful information for pregnant women and healthcare providers, while they support current recommendations of strict clinical surveillance of COVID-19 in late pregnancy and delivery, particularly for symptomatic women.

NOTES

Author contributions: FCro, FC and EG conceived and designed the study. EL, FF and MDGR were responsible of the study protocol at each hospital and guaranteed the correct execution of the study. FCro, FC, and EL were the supervisors at each of the three hospitals for day-to-day running of the study including participant recruitment and data collection. RP, ML, CT, MC, CM were responsible of medical file revision and data collection at the three hospitals involved. CD was responsible of laboratory procedures of antibody analysis. FCro did data analysis. FF supervised the data analysis. FCro, FC and EG drafted the first version of manuscript. EG is the principal investigator the project. All authors critically reviewed and approved the final version of the manuscript.

Additionally, the members of the *KidsCorona Pregnancy COVID-19 group* had the following contribution: AA was responsible of the nursing research team involved in the study; MC, IC, MT, AC, PM, MVB, DB, and AM were residents directly involved in the participants recruitment and data collection at the three hospitals; IM, EC and JM contributed in the collection of first trimester samples; RB, MAM, and JY participated in the antibody analysis; CMA was the microbiologist responsible of the nasopharyngeal RT-PCR data interpretation; CJ, AGO and JM were responsible of sample management and storing; ML and AG were responsible of the clinical management of infected COVID-19 pregnant women; MIR and VF were paediatricians involved in neonatal/postnatal follow-up.

None of them received any compensation for their contribution.

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TABLES

Table 1. Baseline characteristics of the study population according to the presence of SARS-CoV-2 infection

	SARS-CoV-2 negative (n=1,908)	**SARS-CoV-2 positive** (n=317)	**Risk difference (95% CI)**
Age, years	33.3 (29.1-37.1)	33.3 (29-37)	-0.2 (-0.9 to 0.5)
Race or ethnic group			
White	1242 (65.1%)	186 (58.7%)	-6.4% (0.7 to 12.3)
Latin-American	406 (21.3%)	82 (25.9%)	4.6% (-0.3 to 10)
Black	33 (1.7%)	5 (1.6%)	-0.1% (-2 to 1.2)
Asian	129 (6.8%)	26 (8.2%)	1.4% (-1.4 to 5.1)
Others	98 (5.1%)	18 (5.7%)	0.6% (-1.7 to 3.8)
Low socioeconomic status[†]	533 (33.8%)	90 (33.3%)	-0.5% (-5.8 to 6.4)
Smoking during pregnancy	166 (8.7%)	18 (5.7%)	-3% (-0.3 to 5.5)
Comorbidities			
Chronic hypertension	58 (3%)	11 (3.5%)	0.5% (-1.3 to 3.2)
Diabetes mellitus	33 (1.7%)	6 (1.9%)	0.2% (-1 to 2.4)
Obesity[§]	197 (10.3%)	42 (13.2%)	2.9% (-0.7 to 7.3)
Asthma	78 (4.1%)	22 (6.9%)	2.8% (0.3 to 6.2)
Pregnancy history			
Nulliparous	1042 (54.6%)	168 (53%)	-1.6% (-4.3 to 7.5)
Assisted reproductive technologies	146 (7.7%)	24 (7.6%)	-0.1% (-3.5 to 2.9)
Multiple gestation	48 (2.5%)	6 (1.9%)	-0.6% (-1.7 to 1.9)

Data are n (%) or median (IQR).

CI: Confidence interval.

[†]Low socioeconomic status defined as no studies, never worked or unemployment for two years or more; data available for 1,848 cases (1,578 SARS-CoV-2 negative; 270 SARS-CoV-2 positive).

[§]Obesity defined as body mass index >30 kg/m^2.

Table 2. Pregnancy and perinatal outcomes in women with and without evidence of SARS-CoV-2 infection.

	SARS-CoV-2 negative	SARS-CoV-2 positive	Risk difference (95% CI)
Primary outcome			
Overall pregnancy complication[#]	268 (14%)	43 (13.6%)	-0.4% (-4.1 to 4.1)
Early pregnancy complication[†]	15 (1.9%)	2 (1.4%)	-0.5% (-3.2 to 2.1)
Late pregnancy complication[§]	253 (22.4%)	41 (23.3%)	0.9% (-5.3 to 8.1)
Secondary outcomes			
Miscarriage[†]	15 (1.9%)	2 (1.4%)	-0.5% (-3.2 to 2.1)
Abnormal fetal growth† at 20-24 weeks'[¶]	6 (2.6%)	1 (1.9%)	-0.7% (-7.4 to 4)
Fetal malformation at 20-24 weeks'[¥]	16 (3.5%)	3 (3.8%)	0.3% (-3 to 7.2)
Preeclampsia[§]	40 (3.5%)	8 (4.5%)	1% (-1.5 to 5.3)
Preterm delivery[§]	81 (7.2%)	20 (11.4%)	4.2% (-0.03 to 9.9)
Perinatal death[*]	6 (0.5%)	1 (0.6%)	0.1% (-0.7 to 2.7)
Small-for-gestational age[*]	168 (14.5%)	25 (14%)	-0.5% (-5.7 to 5.3)
Intrapartum fetal distress[*]	105 (9.1%)	25 (14%)	4.9% (0.2 to 11)
Admission to high-dependency neonatal care[*]	63 (5.4%)	11 (6.2%)	0.8% (-2.3 to 5.5)
Exploratory outcomes			
Induction of labour[§]	464 (41.1%)	66 (37.5%)	-3.6% (-4.3 to 11)
Caesarean section[§]	311 (27.6%)	54 (30.7%)	3.1% (-3.8 to 10.7)
Gestational age at delivery, weeks[§]	39.3 (2.6)	39.1 (2.1)	-0.2 (-0.6 to 0.2)
Birth weight, g[*]	3198 (609)	3245 (581)	47 (-49 to 143)
Severe small-for-gestational age[*]	55 (4.7%)	8 (4.5%)	-0.2% (-4.1 to 2.8)
Neonatal metabolic acidosis[**]	115 (12.7%)	10 (8.3%)	-4.4% (-2.2 to 8.8)
Maternal breastfeeding[§]	1050 (93.1%)	160 (90.9%)	-2.2% (-1.6 to 7.5)

Data are n (%) or mean (SD). CI: Confidence interval.

[#]Including all pregnancies (n=2,225: 1,908 SARS-CoV-2 negative; 317 SARS-CoV-2 positive)

[†]Including all early pregnancies (n=921: 780 SARS-CoV-2 negative; 141 SARS-CoV-2 positive)

[§]Including all late pregnancies (n=1,304: 1,128 SARS-CoV-2 negative; 176 SARS-CoV-2 positive)

[¶]Data are calculated over 285 consecutive scans completed at the time of data analysis (n=231 SARS-CoV-2 negative, n=54 SARS-CoV-2 positive).

[¥]Data calculated over 540 consecutive scans completed at the time of data analysis (n=460 SARS-CoV-2 negative, n=80 SARS-CoV-2 positive).

[*]Including multiple gestation (n=1,338: 1,1160 SARS-CoV-2 negative; 178 SARS-CoV-2 positive)

[**]Including 1024 neonates (n=903 SARS-CoV-2 negative, n=121 SARS-CoV-2 positive).

Table 3. Pregnancy and perinatal outcomes in women SARS-CoV-2 infected during pregnancy according to the presence or absence of COVID-19 symptoms.

	SARS-CoV-2 negative	SARS-CoV-2 positive		
		asymptomatic	symptomatic	Risk difference (95% CI)
Early pregnancy				
Miscarriage[§]	15 (1.9%)	1 (0.9%)	1 (3.4%)	2.5% (-2.4 to 16.2)
Abnormal fetal growth[†] at 20-24 weeks'[§§]	6 (2.6%)	1 (2.1%)	0 (0%)	-2.1% (-33.4 to 11.1)
Fetal malformation at 20-24 weeks'[§§§]	16 (3.5%)	3 (4.8%)	0 (0%)	-4.8% (-13.9 to 13.1)
Late pregnancy and delivery				
Preeclampsia[¶]	40 (3.5%)	6 (5.6%)	2 (2.8%)	-2.8% (-4.7 to 9.3)
Preterm delivery[¶]	81 (7.2%)	8 (7.6%)	12 (16.9%)[#]	9.3% (-0.4 to 20.3)
Induction of labour[¶]	464 (41.1%)	36 (34.3%)	30 (42.3%)	8% (-6.4 to 22.3)
Intrapartum fetal distress[¥]	105 (9.1%)	11 (10.5%)	14 (19.2%)[†]	8.7% (-1.7 to 20.1)
Caesarean section[¶]	311 (27.6%)	33 (31.4%)	21 (29.6%)	-1.8% (-12.2 to 15.1)
Gestational age at delivery, weeks[¶]	39.1 (2.6)	39.2 (2.1)	39.0 (2.2)	-0.2 (-0.8 to 0.4)
Birth weight, g[¥]	3198 (609)	3299 (535)	3166 (636)	-133 (-307 to 41)
Birth weight centile[¥53]	47 (30.8)	53 (30.6)	51 (32.6)	-0.2 (-11.4 to 7.5)
Small-for-gestational age[¥]	168 (14.5%)	13 (12.4%)	12 (16.4%)	4% (-6.2 to 15.3)
Severe small-for-gestational age[¥]	55 (4.7%)	1 (1%)	7 (9.6%)[*]	8.6% (2.1 to

				17.5)
Neonatal metabolic acidosis[¥¥]	115 (12.7%)	6 (8.1%)	4 (8.5%)	0.4% (-9.5 to 12.6)
Admission to high-dependency neonatal care[¥]	63 (5.4%)	6 (5.7%)	5 (6.8%)	1.1% (-6.2 to 9.8)
Perinatal death[¥]	6 (0.5%)	1 (1%)	0 (0%)	-1% (-4.1 to 5.3)
Maternal breastfeeding[¥]	1050 (93.1%)	96 (91.4%)	64 (90.1%)	-1.3% (-7.2 to 11.1)

Data are n (%) or mean (SD). CI: Confidence interval.

[#]Statistically significant difference between SARS-CoV-2 negative *vs.* positive symptomatic (p=0.003)

[†]Statistically significant difference between SARS-CoV-2 negative *vs.* positive symptomatic (p=0.004)

[*]Statistically significant difference between SARS-CoV-2 positive asymptomatic *vs.* positive symptomatic (p=0.006)

[§]Including all early pregnancies (n=921: 780 negative, 112 positives asymptomatic; 29 positives symptomatic)

[§§]Data are calculated over 285 consecutive scans completed at the time of data analysis (n=231 negative, n=47 positive asymptomatic, n=7 positive symptomatic).

[§§§]Data calculated over 540 consecutive scans completed at the time of data analysis (n=460 negative, n=63 positive asymptomatic, n=17 positive symptomatic).

[¶]Including all late pregnancies (n=1,304: 1,1128 negative, 105 positives asymptomatic; 71 positives symptomatic)

[¥]Including multiple gestation (n=1,338: 1,1160 negative, n= 105 positives asymptomatic; 73 positives symptomatic)

[¥¥]Including 1024 neonates (n=903 negative, n= 74 positives asymptomatic; 47 positives symptomatic)

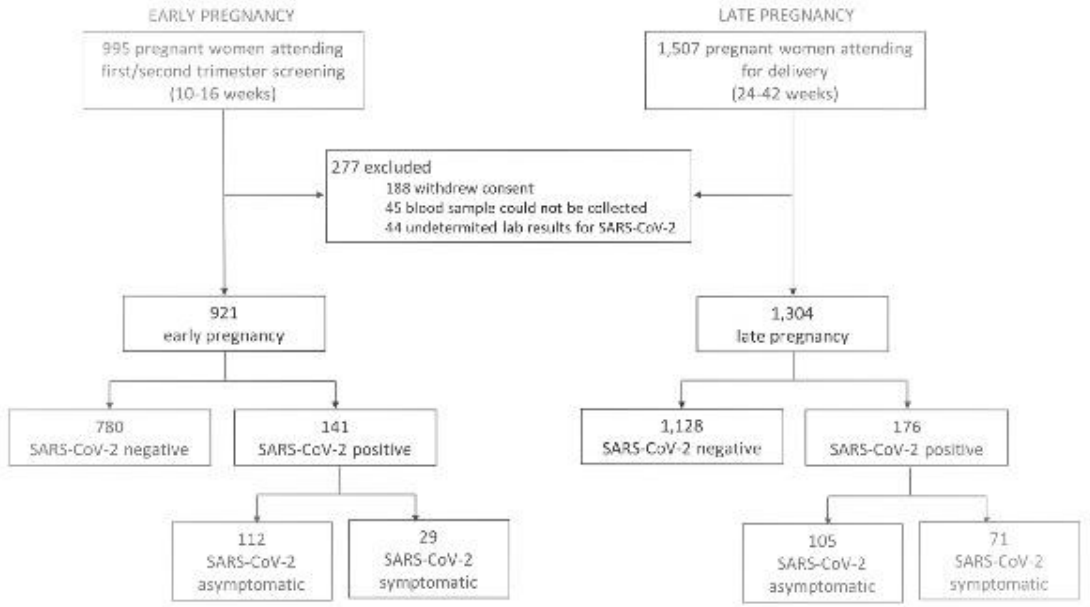
FIGURES LEGENDS

Figure 1. Flowchart of the study population.

Figure 2. Risk difference in primary outcome

Primary outcome was defined as the occurrence of a pregnancy complication (miscarriage, preeclampsia, preterm delivery, perinatal death, small-for-gestational age or admission to high-dependency neonatal care).

Figure 1



Note: Early pregnancies were tested by serology, and late pregnancies by serology and polymerase chain reaction.

Figure 2