OBSTETRICS

Effects of prenatal exposure to maternal COVID-19 and perinatal care on neonatal outcome: results from the INTERCOVID Multinational Cohort Study

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BACKGROUND: The effect of COVID-19 in pregnancy on maternal outcomes and its association with preeclampsia and gestational diabetes mellitus have been reported; however, a detailed understanding of the effects of maternal positivity, delivery mode, and perinatal practices on fetal and neonatal outcomes is urgently needed.

OBJECTIVE: To evaluate the impact of COVID-19 on fetal and neonatal outcomes and the role of mode of delivery, breastfeeding, and early neonatal care practices on the risk of mother-to-child transmission.

STUDY DESIGN: In this cohort study that took place from March 2020 to March 2021, involving 43 institutions in 18 countries, 2 unmatched, consecutive, unexposed women were concomitantly enrolled immediately after each infected woman was identified, at any stage of pregnancy or delivery, and at the same level of care to minimize bias. Women and neonates were followed up until hospital discharge. COVID-19 in pregnancy was determined by laboratory confirmation and/or radiological pulmonary findings or $\geq$2 predefined COVID-19 symptoms. The outcome measures were indices of neonatal and perinatal morbidity and mortality, neonatal positivity and its correlation with mode of delivery, breastfeeding, and hospital neonatal care practices.

RESULTS: A total of 586 neonates born to women with COVID-19 diagnosis and 1535 neonates born to women without COVID-19 diagnosis were enrolled. Women with COVID-19 diagnosis had a higher rate of cesarean delivery (52.8% vs 38.5% for those without COVID-19 diagnosis, $P<.01$) and pregnancy-related complications, such as hypertensive disorders of pregnancy and fetal distress (all with $P<.001$), than women without COVID-19 diagnosis. Maternal diagnosis of COVID-19 carried an increased rate of preterm birth ($P\leq.001$) and lower neonatal weight ($P\leq.001$), length, and head circumference at birth. In mothers with COVID-19 diagnosis, the length of in utero exposure was significantly correlated to the risk of the neonate testing positive (odds ratio, 4.5; 95% confidence interval, 2.2—9.4 for length of in utero exposure >14 days). Among neonates born to mothers with COVID-19 diagnosis, birth via cesarean delivery was a risk factor for testing positive for COVID-19 (odds ratio, 2.4; 95% confidence interval, 1.2—4.7), even when severity of maternal conditions was considered and after multivariable logistic analysis. In the subgroup of neonates born to women with COVID-19 diagnosis, the outcomes worsened when the neonate also tested positive, with higher rates of neonatal intensive care unit admission, fever, gastrointestinal and respiratory symptoms, and death, even after adjusting for prematurity. Breastfeeding by mothers with COVID-19 diagnosis and hospital neonatal care practices, including immediate skin-to-skin contact and rooming-in, were not associated with an increased risk of newborn positivity.

CONCLUSION: In this multinational cohort study, COVID-19 in pregnancy was associated with increased maternal and neonatal complications. Cesarean delivery was significantly associated with newborn COVID-19 diagnosis. Vaginal delivery should be considered the safest mode of delivery if obstetrical and health conditions allow it. Mother-to-child skin-to-skin contact, rooming-in, and direct breastfeeding were not risk factors for newborn COVID-19 diagnosis, thus well-established best practices can be continued among women with COVID-19 diagnosis.

Key words: birthweight, breastfeeding, cesarean delivery, cohort, COVID-19, feeding problems, hospital stay, infections, intrauterine growth restriction, morbidity, mortality, multicenter study, neonatal intensive care unit admission, neonatal outcomes, neonate, neurologic outcome, newborn, perinatal practices, preeclampsia, pregnancy, preterm birth, respiratory support, respiratory symptoms, risk ratio, rooming-in, SARS-CoV-2, SARS-CoV-2 exposure, skin-to-skin, small for gestational age

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Introduction

The COVID-19 pandemic is likely to continue to affect large numbers of pregnant individuals and their offspring. Although immunization programs have reduced infections overall, vaccine hesitancy in pregnancy is common[1,2]; in addition, vaccine availability remains limited, particularly in low-income settings.

Whereas increasing data are becoming available with regard to maternal outcomes associated with COVID-19, less is known about the association with neonatal outcomes.[3] Preliminary reports suggest that SARS-CoV-2 infection in

AJOG at a Glance

Why was this study conducted?

This study aimed to describe and quantify any association between COVID-19 during pregnancy and newborn outcomes, and to assess the safety of perinatal care practices, including breastfeeding, in mothers with a COVID-19 diagnosis.

Key findings

Patients with COVID-19 diagnosis in pregnancy and the postnatal period are at substantial risk of neonatal morbidity and mortality compared with unexposed counterparts, with the most severe effects observed in test-positive neonates born to women with COVID-19 diagnosis. Cesarean delivery was significantly associated with neonatal positivity. Vaginal delivery should be considered as the preferred mode of delivery even in symptomatic women when obstetrical and general health conditions allow it. Mother-to-child skin-to-skin contact, rooming-in, and direct breastfeeding are not risk factors for neonatal test positivity; thus, well-established best evidence-based practices can be continued among women with COVID-19 diagnosis.

What does this add to what is known?

COVID-19 in pregnancy is associated with adverse newborn outcomes; unless otherwise indicated, cesarean delivery should not be the preferred mode of delivery in positive mothers. Skin-to-skin contact and breastfeeding should be encouraged.

the neonatal period causes mild disease without significant impact on newborn health.[4] Considering the deleterious effects on pregnancy of COVID-19[5] and other coronavirus infections,[6] such as severe acute respiratory syndrome (SARS)[7,8] and Middle East respiratory syndrome coronavirus (MERS-CoV),[6,9] a detailed understanding of the effects of COVID-19 on neonatal outcomes is urgently needed.

It is within this context that, in March 2020, the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) initiated INTERCOVID, a prospective, multicountry, multicenter, observational study with the aim of assessing maternal and neonatal outcomes in pregnant individuals with a COVID-19 diagnosis, as compared with concomitantly enrolled pregnant individuals without a COVID-19 diagnosis. The overall effects of COVID-19 on maternal outcomes[10–13] and the association with preeclampsia[14] and gestational diabetes mellitus[15] have recently been reported. The present report focuses on the impact of COVID-19 on neonatal outcomes and the effects of mode of delivery, breastfeeding, and early neonatal care practices on the risk of mother-to-child transmission.[16–18]

Materials and Methods

Study design

From March 2, 2020 to March 18, 2021, we enrolled women from 43 institutions in 18 countries (Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, United Kingdom, and the United States). The distribution by country is presented in Supplemental Figure 1. Data on ethnicity were not collected.

We enrolled a total of 742 women, aged ≥18 years, at any stage of pregnancy or at delivery, with a COVID-19 diagnosis based on: (1) laboratory confirmation of SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) (n=687) and (2) ≥2 predefined COVID-19 symptoms or signs, without laboratory confirmation (n=55). When a woman with COVID-19 diagnosis was identified antenatally, 2 immediately concomitant women without COVID-19 diagnosis aged ≥18 years of similar gestational age (±2 weeks), receiving standard antenatal care, were enrolled on the same day to create an unbiased sample of all pregnant individuals without COVID-19 diagnosis in these institutions. If this was not possible or if the women without COVID-19 diagnosis were lost to follow-up, we enrolled 2 women without COVID-19 diagnosis who were admitted at the same level of care and delivered immediately after the woman with COVID-19 diagnosis. The same selection strategy was used when a woman with COVID-19 diagnosis was identified at hospital admission and delivery was likely during that admission. As a quality check, we confirmed from a biweekly random 10% sample that the 2 women without COVID-19 were appropriately chosen; we excluded 5 women with COVID-19 diagnosis and the corresponding women without COVID-19 diagnosis where such confirmation was missing.[11]

For the present analysis, we excluded mother–newborn dyads when the neonate was not tested for COVID-19 even if clinically indicated, or when the reason was not clearly described.

Live and stillborn and singleton and multiple pregnancies were included, along with even those with congenital anomalies. In keeping with reporting requirements during the pandemic, we excluded mothers and newborns from the final analysis if their data had already been published in any comparative study with women without COVID-19 diagnosis, other than INTERCOVID-related papers.

The Oxford Tropical Research Ethics Committee and all local ethics committees approved the study. Informed consent (oral or written) was obtained from participants according to local requirements, except when a waiver or exemption from such consent was granted by a local committee. We adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol, including the laboratory tests used, has been previously published.[11]

Outcomes definition

The primary outcome was the association between maternal COVID-19 exposure and neonatal positivity; the secondary outcome was the association of time of exposure, mode of delivery, breastfeeding, and neonatal care practices with neonatal outcomes.

Data on maternal and pregnancy history, delivery mode, indication for cesarean delivery, newborn outcomes, and feeding practices were collected with standardized forms used in the INTERGROWTH-21st project.[19] In addition, we recorded detailed data on each mother's health and condition at admission, perinatal management, and in-hospital practices (eg, skin-to-skin contact, isolation from the neonate, and use of masks and hand washing by mothers and hospital staff). We also recorded information regarding the timing and results of SARS-CoV-2 testing and COVID-19—related symptoms for mothers and neonates.

Gestational age estimation was based on ultrasound measurement of fetal crown-rump length (<14 weeks' gestation).[20] If early ultrasound dating was not performed, the "best obstetrical" estimate was used based on all clinical and ultrasound data available at the time of delivery.

The total time of exposure to SARS-CoV-2 was defined as the number of days between the woman testing positive or the onset of symptoms and delivery. We chose a 10-day cutoff to study the risk in different populations (ie, women still infectious during labor and women most probably not infectious during labor) given that the horizontal infectiousness of patients with symptoms or a positive test >10 days before labor onset seems very low.[21,22] The maternal symptom severity score was defined as a continuous variable composed of the sum of preset values attributed to each maternal COVID-19—related symptom, according to the severity of the symptom.

In the data collection form, the indications for delivery that are often used in medical records were recorded. For the analyses, in mothers who delivered by cesarean delivery, those indications were grouped into potentially COVID-19—related and others. We included in the potentially COVID-19—related indications hypertensive disorders of pregnancy,[14] fetal distress, fetal growth restriction, suspected smallness for gestational age (SGA) or fetal growth restriction,[6] premature rupture of membranes, and infections. SGA was defined as being born with weight below the 10th percentile on the basis of INTERGROWTH-21st international standards for newborn weight.[23]

Newborn weight, length, and head circumference were assessed against the international INTERGROWTH-21st standards following a standardized protocol. Measurement instruments were regularly calibrated and used by trained staff. Data on neonatal health outcomes, diagnostics, and treatments were collected in detail and grouped into the following categories: (1) neurologic problems including seizures, hydrocephalus, neurologic disorders, any hypoxic-ischemic encephalopathy, and periventricular hemorrhage/leukomalacia grade 3 or 4 per Papile criteria; (2) gastrointestinal conditions including no enteral feeding for >24 hours, necrotizing enterocolitis, stoppage of enteral feeding for >3 consecutive days, gastroesophago-pharyngeal reflux, persistent vomiting, and diarrhea; (3) infections including sepsis, hypotension requiring inotropic steroids, and pneumonia or acute respiratory infections; and (4) respiratory conditions including pneumonia or bronchiolitis, apnea of prematurity, bronchopulmonary dysplasia (BPD), and corticosteroids for BPD.

Detailed data regarding feeding were recorded and included: type of feeding, that is, any breastfeeding (defined as exclusive or partial breastfeeding) and no breastfeeding (defined as exclusive formula or only parenteral nutrition); and mode of feeding, that is, direct breastfeeding, bottle feeding, or tube feeding. Furthermore, information regarding hospital newborn care practices, including immediate skin-to-skin contact, rooming-in, and hygiene measures were recorded for neonates tested for COVID-19. All data were collected on newborn care forms during hospital stay and at discharge.

Because of the unavailability of COVID-19 testing kits at various times in different countries, it was not possible to standardize newborn testing policies. A list of the diagnostic tests used to assess maternal and neonatal COVID-19 status across the participating countries is available in the Study Documents on the INTERCOVID website.[19] Whereas most centers tested all newborns from mothers with COVID-19 diagnosis, a few tested only newborns with clinical signs, such as fever, respiratory distress, or need for respiratory support. The analysis was therefore conducted in 3 different groups born to women with a COVID-19 diagnosis: (1) neonates who tested negative for COVID-19 (99.7% tested using RT-PCR); (2) neonates who had no clinical signs of COVID-19 and were not tested; and (3) neonates who tested positive for COVID-19 (92.7% tested using RT-PCR).

Statistical analysis

We used chi-square tests for proportions and *t*-tests for continuous variables to compare maternal baseline characteristics and early outcomes between neonates born to mothers with and without a COVID-19 diagnosis; similarly, for neonatal characteristics and other outcomes, we compared the 3 groups of neonates. We used negative binomial models to calculate relative risks for neonatal outcomes among the 3 groups; neonates born to mothers without COVID-19 diagnosis were the reference group. We adjusted for the following covariates that were selected using directed acyclic graphs[24]: maternal age, tobacco use, parity, history of pregnancy complications, and gestational age. To complement the crude, unadjusted analysis, we explored logistic regression

TABLE 1
Maternal COVID-19 diagnosis, neonatal COVID-19 test status, and maternal baseline characteristics in the INTERCOVID study

		Mothers with COVID-19 diagnosis			
Maternal characteristics	Mothers without COVID-19 diagnosis (n=1500) n (%) or mean±SD	All mothers with COVID-19 diagnosis (n=569) n (%) or mean±SD	Neonate COVID-19 negative (n=353) n (%) or mean±SD	Neonate without signs not tested (n=163) n (%) or mean±SD	Neonate COVID-19 positive (n=53) n (%) or mean±SD
Maternal age, mean±SD	30.3±6.1	29.8±6.1	30.2±6.2	28.8±5.6	29.7±6.8
Maternal smoking	60 (4.0)	16 (2.8)	12 (3.5)	2 (1.2)	2 (3.8)
Previous preterm birth	81 (6.1)	38 (7.6)	24 (7.9)	10 (6.8)	4 (8.2)
Previous low birthweight newborn	104 (7.8)	45 (9.2)	25 (8.3)	15 (10.2)	5 (10.2)
Previous neonatal death	41 (3.1)	29 (5.8)[a]	16 (5.3)	10 (6.8)	3 (6.1)
Prenatal multivitamins/minerals	702 (47.1)	286 (51.6)	179 (2.0)	74 (47.1)	33 (62.3)
Gestational diabetes mellitus	125 (8.4)	66 (11.6)[a]	34 (9.7)	26 (16.1)	6 (11.3)
Maternal hypertension, preeclampsia, or eclampsia	140 (9.4)	85 (15.0)[a]	50 (14.2)	26 (16.0)	9 (17.0)
Premature rupture of membranes	271 (18.5)	92 (16.6)	59 (17.0)	25 (16.1)	8 (15.1)
Prophylactic corticosteroids	83 (5.7)	66 (12.0)[a]	43 (12.5)	14 (9.0)	9 (17.0)
Fetal distress	122 (8.2)	72 (12.7)[a]	49 (13.9)	14 (8.6)	9 (17.0)
Cesarean delivery	576 (38.5)	300 (52.8)[a]	165 (46.9)	98 (60.1)	37 (69.8)
Induced labor	336 (22.4)	123 (21.6)	82 (23.2)	33 (20.3)	8 (15.1)
Preterm birth	200 (13.4)	132 (23.2)[b]	83 (23.5)	32 (19.8)	17 (32.1)
Medically-indicated preterm birth	130 (8.7)	113 (19.9)[b]	70 (19.8)	26 (16.1)	17 (32.1)

SD, standard deviation.

[a] $P \leq .01$; [b] $P \leq .001$, comparing neonates born to mothers with COVID-19 diagnosis with neonates born to mothers without COVID-19 diagnosis.

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models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for neonates testing positive for COVID-19 stratified by the number of days between maternal diagnosis and delivery, and adjusting for mode of delivery for comparison.

Among neonates tested for COVID-19 and born to women with COVID-19 diagnosis, we collected complete information from newborn care forms to determine if factors during delivery and after birth were related to the neonates testing positive. We used chi-square tests to compare the reasons for cesarean delivery among neonates that tested positive vs negative for COVID-19 born to women with COVID-19 diagnosis. We used logistic regression models to calculate ORs and 95% CIs for predictors of the neonates testing positive for COVID-19. We stratified by the time between diagnosis and delivery (≤24 hours or >24 hours) and used chi-square tests to evaluate delivery outcomes, neonatal outcomes, and newborn care practices. Finally, for sensitivity analysis we assessed the associations between neonatal COVID-19 status and neonatal outcomes among neonates born to mothers with a positive COVID-19 test only.

Results

We enrolled a total of 742 women with a COVID-19 diagnosis based on: (1) laboratory confirmation of SARS-CoV-2 infection by RT-PCR (n=687) and (2) ≥2 predefined COVID-19 symptoms or signs, without laboratory confirmation (n=55). Mother−newborn dyads in which the neonate was not tested for COVID-19 were excluded (n=180 neonates and 173 mothers).

Therefore, we included in this analysis 569 women with and 1500 women without COVID-19 diagnosis. Because multiple pregnancies were included, a total of 586 newborns of mothers with COVID-19 diagnosis and 1535 newborns of mothers without COVID-19 diagnosis were included, all with broadly similar demographic characteristics to those described in previous papers. Supplemental Figure 2 provides the study enrollment flowchart.

Table 1 presents maternal baseline characteristics for women with and without COVID-19 diagnosis, with the former group subdivided into those with neonates who tested positive or negative for COVID-19 and those with neonates without clinical signs who were not tested. Women with COVID-19 diagnosis had higher rates of hypertensive disorders of pregnancy and pregnancy-induced hypertension, and higher occurrence of gestational diabetes mellitus, previous neonatal death, previous preterm birth, and previous low birthweight newborns than women without COVID-19 diagnosis. Compared with those without COVID-19 diagnosis, pregnant persons with COVID-19 diagnosis had higher incidence of cesarean delivery, preterm birth, medically-indicated preterm birth, and related prophylactic antenatal corticosteroid therapy given for fetal lung maturation, all with $P<.01$, reflecting higher rates of pregnancy complications in this group. For all these variables, women with COVID-19 diagnosis had higher rates ($P<.01$) than women without COVID-19 diagnosis.

Women with COVID-19 diagnosis had a cesarean delivery rate (Table 1) of 52.8% vs 38.5% for those without COVID-19 diagnosis ($P<.01$). Among women with COVID-19 diagnosis, those with neonates that tested positive for COVID -19 had a cesarean delivery rate of 69.8% vs 46.9% for those with neonates who tested negative ($P<.01$). Reasons for cesarean delivery did not significantly differ between groups, neither individually nor when grouped by COVID-19—related indications vs other indications (Supplemental Table 1). In a multivariable logistic regression analysis (Supplemental Table 2) including time of exposure and immediate mother—newborn skin-to-skin contact, birth via cesarean delivery was statistically significantly associated with neonates testing positive for COVID-19 (adjusted OR [aOR], 2.4; 95% CI, 1.2—4.7).

Moreover, we investigated if cesarean delivery was independently associated with neonatal positivity and found no interaction between direct breastfeeding and cesarean delivery (P-interaction=.93). In addition, the interaction term between skin-to-skin contact and cesarean delivery was marginally significant (P-interaction=.17). With skin-to-skin contact and the interaction between skin-to-skin contact and cesarean delivery in the model, the OR for neonates testing positive with cesarean delivery increased to 3.4 (1.4—8.2), but the CIs were much wider.

As presented in Table 1, fetal distress was lowest in neonates of women without COVID-19 diagnosis, higher among COVID-19—negative neonates of women with COVID-19 diagnosis, and highest among COVID-19—positive neonates whose mothers also had a COVID-19 diagnosis.

Table 2 presents early neonatal outcomes by maternal COVID-19 diagnosis and neonatal test status. Among the newborns of women with COVID-19 diagnosis (including multiple births), 366 (62.5%) tested negative (99.7% tested with RT-PCR), 56 (9.5%) tested positive (92.7% tested with RT-PCR), and 164 (28%) had no clinical signs and were not tested. Among COVID-19—positive neonates of women with COVID-19 diagnosis, the time between maternal diagnosis and delivery was significantly longer than in the group of COVID-19—negative neonates (13.3 days vs 6.4 days, $P=.007$), whereas the gestational age at diagnosis was significantly lower (35.3 weeks vs 37 weeks, $P=.002$).

Figure shows the ORs and 95% CIs for the COVID-19—positive neonates by the time elapsed between maternal diagnosis and delivery, adjusted for cesarean delivery. The aORs increased with the time between diagnosis and delivery, particularly after 7 days (aOR, 2.0; 95% CI, 1—3.7; $P=.04$) and 14 days of exposure (aOR, 4.5; 95% CI, 2.2—9.4; $P<.001$) (Supplemental Table 3).

As shown in Table 2, we did not observe any significant differences in severity and number of maternal symptoms across the 3 neonatal groups with mothers with COVID-19 diagnosis. COVID-19—positive neonates born to women with COVID-19 diagnosis had on average >1 week lower gestational age at birth than those born to women without COVID-19 diagnosis (Table 2). Thus, birthweight, length, and head circumference were on average lower among COVID-19—positive neonates born to women with a COVID-19 diagnosis than among those born to women without COVID-19 diagnosis. The rates of fetal distress in labor, neonatal intensive care unit (NICU) admission, and early neonatal complications and morbidities among COVID-19—positive newborns of women with COVID-19 diagnosis were also higher than those of newborns of mothers without COVID-19 diagnosis. NICU admission and early neonatal complications were also higher in COVID-19—negative newborns born to women with COVID-19 diagnosis than in those born to women without COVID-19 diagnosis (Table 2).

Table 3 shows outcomes up to hospital discharge of COVID-19—negative, COVID-19—positive, and untested neonates of women with COVID-19 diagnosis. A NICU stay longer than 7 days occurred significantly more frequently in COVID-19—positive than in COVID-19—negative neonates. The proportion of any breastfeeding did not differ significantly between those who tested negative vs positive. However, a higher proportion of breastfeeding, both during hospital stay and at discharge, was observed in untested neonates, in whom the rate of respiratory problems and infections was significantly lower than that of COVID-19—negative neonates of women with COVID-19 diagnosis. In contrast, COVID-19—positive neonates had significantly higher rates of complications such as fever, infections, respiratory problems, or need for respiratory support than COVID-19—negative neonates (Table 3).

Table 4 shows the increased relative risks for most neonatal outcomes, comparing neonates born to mothers with COVID-19 diagnosis with those born to mothers without COVID-19 diagnosis. As expected, relative risks were higher in the subgroup of neonates who tested positive, after correction for maternal risk factors and gestational age. In particular, we found a higher risk of respiratory (OR, 3.4; 95% CI, 2.2—5.3), neurologic (OR, 4.9; 95% CI, 1.7—14.1), and gastrointestinal (OR, 5.9; 95% CI, 2.1—16.6) signs, and NICU stays longer than 7 days (OR, 5.4; 95% CI, 3.2—9.1) among COVID-19—positive neonates than among those with a mother

TABLE 2

Maternal COVID-19 diagnosis, neonatal COVID-19 test status, and early outcomes in the INTERCOVID study

		Mother with COVID-19 diagnosis		
Neonatal characteristics	Mother without COVID-19 diagnosis (n=1535)[a] n (%) or mean±SD	Neonates COVID-19 negative (n=366)[a] n (%) or mean±SD	Neonates without signs not tested (n=164)[a] n (%) or mean±SD	Neonates COVID-19 positive (n=56)[a] n (%) or mean±SD
Total time of exposure (days from positive swab to delivery)[b]	NA	6.4 ± 16.4	16.4 ± 34.0[c]	13.3 ± 23.8[c]
Positive at delivery = total time of exposure (days from positive swab to delivery) ≤10	NA	314 (88.7)	100 (73.5)	38 (67.9)
Gestational age at diagnosis	NA	37.0±3.5	35.7±2.9[d]	35.3±4.5[d]
Any maternal symptoms	NA	178 (48.6)	103 (62.8)	30 (53.6)
Maternal symptom severity score[b]	NA	4.3±5.7	5.7±6.3	5.0±6.7
Number of maternal symptoms[b]	NA	1.4±1.8	1.8±1.9	1.7±2.2
Days of maternal symptoms[b]	NA	7.7±14.4	7.9±14.1	10.6±16.7
Maternal radiological signs	NA	74 (20.6)	21 (13.5)	8 (14.6)
Mother admitted to ICU	25 (1.6)	35 (9.6)	7 (4.3)	4 (7.1)
Gestational age at delivery[b]	38.5±3.2	37.8±2.8	38.0±2.8	37.3±3.6[e]
Testing within 24 h after birth	NA	195 (53.3)	NA	26 (46.4)
Testing within 48 h after birth	NA	276 (75.4)	NA	40 (71.4)
Male sex (%)	804 (52.8)	185 (50.6)	84 (51.5)	29 (52.7)
Birthweight (kg)[b]	3.09±0.67	2.92±0.69	2.96±0.64	2.79±0.84[e]
Birth length (cm)[b]	49.1±3.9	48.4±4.1	48.6±5.1	47.2±5.7[d]
Head circumference at birth (cm)[b]	34.1±2.1	33.6±2.2	34.1±2.4	33.2±2.7[d]
Birthweight SDS[b]	−0.02±1.07	−0.07±1.09	−0.11±1.17	−0.15±1.13
Birth length SDS[b]	0.40±1.27	0.37±1.29	0.51±1.39	0.22±1.28
Head circumference at birth SDS[b]	0.53±1.15	0.53±1.14	0.59±1.19	0.45±1.15
5-min Apgar score	9.0±1.7	9.1±1.2	8.6±2.0	8.8±1.7
5-min Apgar score <7	61 (4.0)	16 (4.4)	10 (6.2)	4 (7.1)
Intrauterine distress	96 (6.3)	35 (9.6)	12 (7.3)	9 (16.1)[e]
Meconium aspiration	8 (0.5)	5 (1.4)	0 (0.0)	2 (3.7)[e]
NICU admission (%)	164 (10.8)	121 (33.5)[e]	15 (9.4)	28 (50.0)[e]
Days in NICU (median and IQR)	5 (1−12)	4 (2−12)	3 (2−7)	7 (3−13)
Respiratory distress syndrome	74 (4.9)	37 (10.2)[e]	8 (5.0)	9 (16.1)[e]
Transient tachypnea of newborn	39 (2.6)	25 (6.9)[d]	6 (3.7)	7 (12.5)[e]

ICU, intensive care unit; *IQR*, interquartile range; *NA*, not applicable; *NICU*, neonatal intensive care unit; *SD*, standard deviation; *SDS*, standardized score.

[a] Numbers are different from Table 1 because of twin births; [b] Mean ± SD; [c] $P \leq .01$ comparing each category from mothers with COVID-19 diagnosis (untested neonates without signs and positive neonates) separately to negative neonates born to mothers with COVID-19 diagnosis; [d] $P \leq .01$; [e] $P \leq .001$ comparing each category from mothers with COVID-19 diagnosis (negative neonates, untested neonates without signs, and positive neonates) separately to neonates born to mothers without COVID-19 diagnosis.

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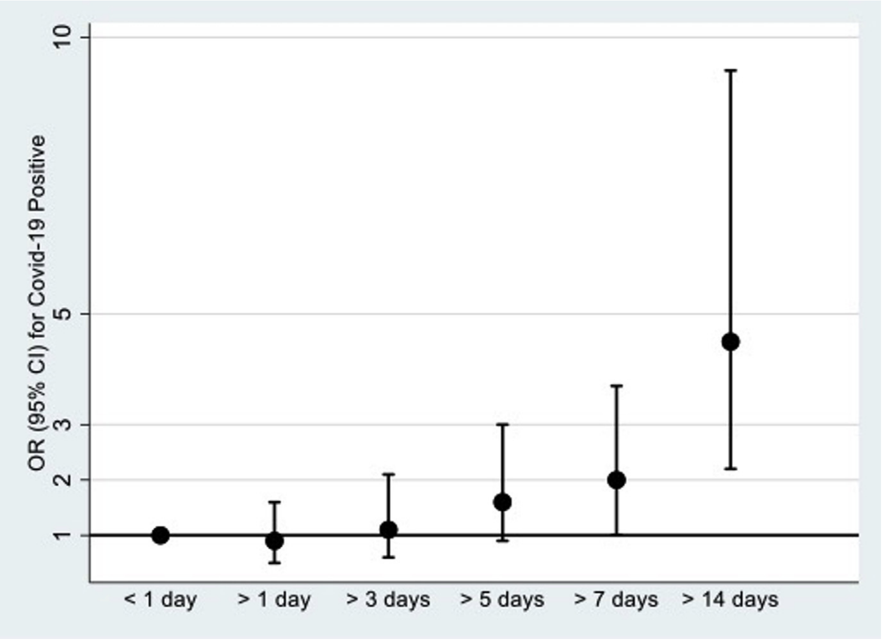
without COVID-19 diagnosis. The results were similar, although the CIs were wider, when we restricted this analysis only to mothers who tested positive for COVID-19 (Supplemental Tables 4−7).

Table 5 provides data regarding care practices for neonates of mothers with COVID-19 diagnosis. Immediate skin-to-skin contact was less frequent in COVID-19−positive than in COVID-19−negative neonates. There were no differences in frequency of rooming-in with the mother, mask wearing and hand washing by mothers and hospital staff before touching the neonate, or the

FIGURE
Adjusted ORs and 95% CIs for neonates testing positive between maternal COVID-19 diagnosis and delivery



CI, confidence interval; *OR*, odds ratio.

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proportion of neonates who received breast milk. We specifically explored the association between human milk feeding regimens and neonatal COVID-19 test positivity, and the risk of transmission of SARS-CoV-2 by breastfeeding vs expressed human milk feeding. Any breastfeeding compared with exclusive formula or no oral feeding was not associated with neonatal test positivity. We did not find any differences in the risk of being COVID-19—positive between neonates receiving direct breastfeeding and those receiving donor milk or extracted mother's breast milk administered by bottle.

Comment

Principal findings

This large-scale, prospective, multinational study assessed the association between COVID-19 diagnosis in pregnancy and maternal and neonatal outcomes. We have previously provided evidence of the risk associated with a COVID-19 diagnosis during pregnancy.[11] Here, we concentrate on the effect of neonatal and perinatal practices on outcomes, with a particular focus on topics of interest for clinical practice, such as the indication for mother—newborn separation after birth in case of the mother testing positive, the effectiveness of preventive measures, and the safety of breastfeeding. We also present data regarding the associations between in utero exposure, type of delivery, and the neonatal risk of testing positive for COVID-19, and the association between maternal COVID-19 diagnosis and neonatal morbidity. A COVID-19 diagnosis in pregnancy and the postnatal period carries a substantial risk of neonatal morbidity and mortality. Cesarean delivery was significantly associated with neonatal COVID-19 test positivity. Mother-to-child skin-to-skin contact, rooming-in, and direct breastfeeding are not risk factors for neonatal test positivity.

Results in the context of what is known and clinical implications

Overall, a maternal diagnosis of COVID-19 greatly influenced perinatal and neonatal outcomes, with increased rates of preterm birth and lower weight, length, and head circumference at birth. Respiratory signs and NICU admission were also more common among neonates born to women with COVID-19 diagnosis. Hence, we have demonstrated a direct impact on the newborn, secondary to maternal infection, independent of neonatal test positivity or negativity. Moreover, as expected, COVID-19—positive neonates of women with COVID-19 diagnosis, compared with neonates that tested negative, had increased rates of prolonged NICU stay, fever, gastrointestinal and respiratory problems, and death, even after adjusting for prematurity, which suggests a direct effect of SARS-CoV-2 infection on neonatal morbidity.

In women with COVID-19 diagnosis, there was a significant correlation between the length of in utero exposure and risk of the neonate testing positive. In women with COVID-19 diagnosis, the gestational age at maternal diagnosis was significantly lower in neonates who tested positive at birth than in those who tested negative (35.3 weeks vs 37 weeks). However, the time between maternal diagnosis and delivery was significantly longer in COVID-19—positive than in COVID-19—negative neonates (13.3 days vs 6.4 days), resulting in a similar mean gestational age at birth.

The pathogenic mechanisms that could explain the correlation between the total time of exposure and risk of neonatal positivity are yet to be elucidated.[25] In general, it is considered that vertical transmission with SARS-CoV-2 does not occur prenatally. However, the fact that SARS-CoV-2's cellular receptor, angiotensin converting enzyme-2 (ACE-2), has been detected in the placenta, albeit at a low level, raises the possibility of transplacental transmission[26] in some rare cases. Once SARS-CoV-2 binds to the ACE-2 receptor, the transmembrane protease, serine 2 enzyme (TMPRSS2) is activated and allows the virus to pass into the cell; TMPRSS2 is expressed after 24 weeks' gestation.[27] Conflicting data exist on the extent of coexpression.[28,29] Viremia is also associated with vascular damage, including hypercoagulability

TABLE 3
Neonatal outcomes of neonates born to mothers with and without COVID-19 diagnosis in the INTERCOVID Study

		Mother with COVID-19 diagnosis		
Neonatal outcomes	Mother without COVID-19 diagnosis (n=1535)[a] n (%)	Neonate COVID-19 negative (n=366) n (%)	Neonate without signs not tested (n=164) n (%)	Neonate COVID-19 positive (n=56) n (%)
Congenital malformation	63 (4.2)	11 (3.0)	2 (1.2)	1 (1.8)
Neurologic conditions[a]	20 (1.3)	11 (3.0)	0 (0.0)[b]	4 (7.1)
Anemia requiring transfusion	8 (0.5)	9 (2.5)	0 (0.0)[b]	1 (1.8)
Fever	6 (0.4)	2 (0.6)	0 (0.0)	4 (7.1)[c]
Gastrointestinal conditions[d]	22 (1.4)	6 (1.6)	0 (0.0)	5 (8.9)[c]
Infections[e]	123 (8.0)	63 (17.2)	18 (11.0)	13 (23.2)
Antibiotics	101 (6.6)	51 (14.1)	12 (7.5)[b]	9 (16.1)
Respiratory conditions[f]	121 (7.8)	69 (18.9)	14 (8.5)[g]	17 (30.4)[b]
Respiratory support ≤48 hours	74 (4.8)	29 (7.9)	12 (7.3)	10 (17.9)[b]
Respiratory support >48 hours	45 (2.9)	33 (9.0)	2 (1.2)[c]	8 (14.2)
Any other serious condition	46 (3.0)	11 (3.0)	4 (2.5)	5 (8.9)[b]
NICU >7 days	68 (4.5)	49 (13.7)	4 (2.5)[c]	15 (26.8)[g]
Death	23 (1.5)	1 (0.3)	4 (2.4)[b]	2 (3.6)[g]
Days at full oral feeding >1	100 (8.3)	55 (19.5)	14 (11.5)[b]	13 (25.5)
Any breastfeeding during hospitalization	1,083 (83.6)	254 (77.0)	130 (89.0)[g]	42 (79.3)
Any breastfeeding at discharge	1,329 (91.0)	288 (80.5)	138 (92.0)[c]	42 (75.0)

BPD, bronchopulmonary dysplasia; *NICU*, neonatal intensive care unit.

[a] Neurologic problems include seizures, hydrocephalus, neurologic disorders, hypoxic-ischemic encephalopathy, periventricular hemorrhage/leukomalacia; [b] $P \leq .05$; [c] $P \leq .001$ compared with mothers with COVID-19 diagnosis, child COVID-19 negative; [d] Gastrointestinal conditions include no enteral feeding for >24 hours, necrotizing enterocolitis, stoppage of enteral feeding for more than 3 consecutive days, gastro-esophago-pharyngeal reflux, persistent vomiting, and diarrhea; [e] Infections include sepsis, hypotension requiring inotropics/steroids, and pneumonia/acute respiratory infections; [f] Respiratory conditions include pneumonia/bronchiolitis, apnea of prematurity, BPD, and corticosteroids for BPD; [g] $P \leq .01$.

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and poor vascular perfusion[30]; the resulting placental damage could facilitate such vertical transmission.[25]

The cesarean delivery rate was significantly higher in women with COVID-19 diagnosis than in those without, possibly because obstetricians adopted a more interventional approach to the affected women. However, when we focused on women with COVID-19 alone, the cesarean delivery rate was still significantly higher in COVID-19—positive (71.4%) than in COVID-19—negative (48.9%) neonates. Analysis of both cesarean delivery COVID-19—related indications and the severity of maternal conditions did not show any differences between the COVID-19—positive and negative neonates, which reinforces the independence of cesarean delivery in determining neonatal positivity, as confirmed also by multivariable logistic analysis. There is no clear explanation for this observation, although one interesting hypothesis is that neonates born by cesarean delivery have less immediate contact with the mother, with consequently less intake of colostrum, which is very rich in immunologic protective factors,[31] and thus increased risk of SARS-CoV-2 infection. At present, these exploratory data do not support a recommendation for cesarean delivery in mothers with COVID-19 diagnosis.

Another important finding was that breastfeeding in mothers with COVID-19 diagnosis was not associated with increased risk for neonatal test positivity. Therefore, given the additional well-known benefits of mother's milk on neonatal health, we strongly recommend that all measures to promote, protect, and sustain breastfeeding be maintained in mothers with COVID-19 diagnosis, as indicated by the World Health Organization and Centers for Disease Control and Prevention guidelines.[32,33] Interestingly, in this large and multicultural study, rates of breastfeeding during hospital stay and at discharge were similar in test-positive and negative neonates. Considering the initial uncertainty in the setting of a global pandemic, this is a positive finding about the commitment to breastfeeding in our populations, and it allowed us to have a good number of breastfed newborns in this study.

Finally, the data collected on neonatal care practices showed that immediate skin-to-skin contact and rooming-in did not increase the risk of neonatal test

TABLE 4
Adjusted[a] relative risks for neonatal COVID-19 test status and neonatal outcomes among neonates born to mothers with COVID-19 diagnosis in the INTERCOVID Study

Outcome	Neonate COVID-19 negative aRR (95% CI)	Neonate without signs not tested aRR (95% CI)	Neonate COVID-19 positive aRR (95% CI)
Any respiratory conditions	2.4 (1.8—3.1)	1.1 (0.6—1.8)	3.4 (2.2—5.3)
Respiratory support	2.2 (1.7—2.9)	1.0 (0.6—1.8)	3.3 (2.2—5.1)
Neurologic conditions	2.4 (1.1—5.0)	Not observed[b]	4.9 (1.7—14.1)
Feeding problems	1.6 (1.0—2.6)	0.5 (0.1—1.5)	3.2 (1.7—6.2)
Anemia requiring transfusion	6.1 (2.0—18.3)	Not observed[b]	4.1 (0.5—32.5)
Fever	1.7 (0.2—18.1)	Not observed[b]	21.1 (5.2—85.1)
Gastrointestinal conditions	1.2 (0.5—2.9)	Not observed[b]	5.9 (2.1—16.6)
Infections	2.2 (1.6—2.9)	1.4 (0.8—2.2)	2.7 (1.6—4.4)
Antibiotics	2.1 (1.5—2.9)	1.0 (0.6—2.0)	2.2 (1.2—3.8)
NICU $\geq$7 d	3.1 (2.1—4.5)	0.4 (0.1—1.2)	5.4 (3.2—9.1)

aRR, adjusted relative risk; *CI*, confidence interval; *NICU*, neonatal intensive care unit.

[a] Reference group was mothers without COVID-19 diagnosis, adjusted for maternal age, tobacco use, parity, history of pregnancy complications, and gestational age; [b] Relative risk not estimated, no cases.

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TABLE 5
Characteristics of newborn care among neonates that tested negative and positive for COVID-19 born to mothers with COVID-19 diagnosis in the INTERCOVID Study

	Mother with COVID-19 diagnosis	
Characteristic	Neonate COVID-19 negative (n=358) n (%)	Neonate COVID-19 positive (n=55) n (%)
Immediate skin-to-skin contact	147 (41.1)	12 (21.8)[a]
Newborn isolated from mother	173 (48.1)	27 (49.1)
Mother wore a mask	323 (89.7)	51 (92.3)
Mother washed hands before touching the newborn	318 (89.3)	46 (85.2)
Hospital policy of staff wearing mask and gloves	355 (98.6)	55 (100)
Direct breastfeeding	273 (74.6)	40 (71.4)
Breast milk, no breastfeeding	29 (8.8)	5 (9.4)
Oral feeding, no breast milk	42 (12.7)	7 (13.2)

**$P\leq$.001 compared with COVID-19—negative neonates.

[a] $P\leq$0.01.

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positivity in settings where mothers wore masks and washed their hands before touching their neonates and the hospital staff used gloves and masks. This is an important result because some hospitals have adopted policies that discourage immediate skin-to-skin contact or keep the neonate isolated from mothers with COVID-19 diagnosis, especially early in the pandemic.[34,35] Our data show that these are unnecessary practices and can deprive the mother and her neonate of the well-recognized beneficial effects of early contact, such as closer bonding, early initiation and continuation of breastfeeding, and reduced infections.[36]

Strengths and limitations

Our study has expected limitations. Regarding selection of the population, by selecting a reference group of 2 women recruited immediately after each woman with COVID-19 diagnosis at the same level of care, we were able to obtain results rapidly and reduce systematic bias despite the lack of widely available COVID-19 tests until late 2020. However, we recognize that a few asymptomatic affected women may have been included in the control group, but this conservative bias would eventually underestimate the effect of the COVID-19 infection; in our opinion, this confirms even further the differences identified between the groups.

We acknowledge the risk of ascertainment bias in reporting maternal and neonatal morbidity given that the newborns of women with COVID-19 diagnosis may have been more strictly monitored than those of women without COVID-19 diagnosis, and adverse events noted more rigorously. However, this limitation would not explain differences in outcomes between test-positive and test-negative neonates from the homogeneous population of mothers with COVID-19 diagnosis. Another limitation is that, because of the global unavailability of testing kits, it was not possible to standardize neonatal testing policies or to take swabs from all newborns. More general limitations related to study design have been previously addressed and discussed.[11,37]

Conclusions

In summary, patients with COVID-19 diagnosis in pregnancy and the postnatal period are at substantial risk of neonatal morbidity and mortality compared with counterparts without COVID-19 diagnosis, with the most severe effects observed in test-positive neonates born to women with COVID-19 diagnosis.

Cesarean delivery was significantly associated with neonatal COVID-19 test positivity. Vaginal delivery should be considered as the preferred mode of delivery even in symptomatic women when obstetrical and general health conditions allow it. Mother-to-child skin-to-skin contact, rooming-in, and direct breastfeeding are not risk factors for neonatal test positivity; thus, well-established best evidence-based practices can be continued among women with COVID-19 diagnosis. ■

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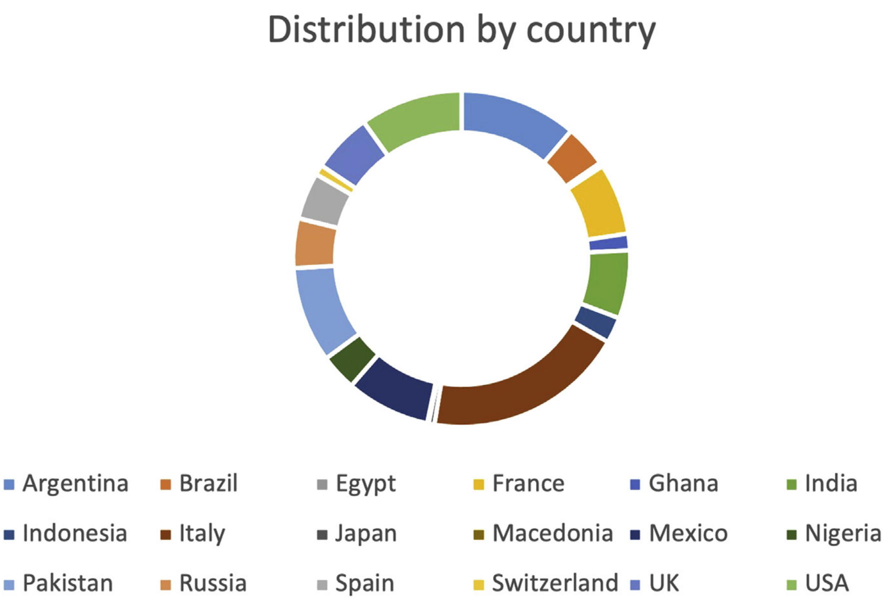
Appendix

SUPPLEMENTAL FIGURE 1
Distribution of mothers with COVID-19 diagnosis by country, INTERCOVID study



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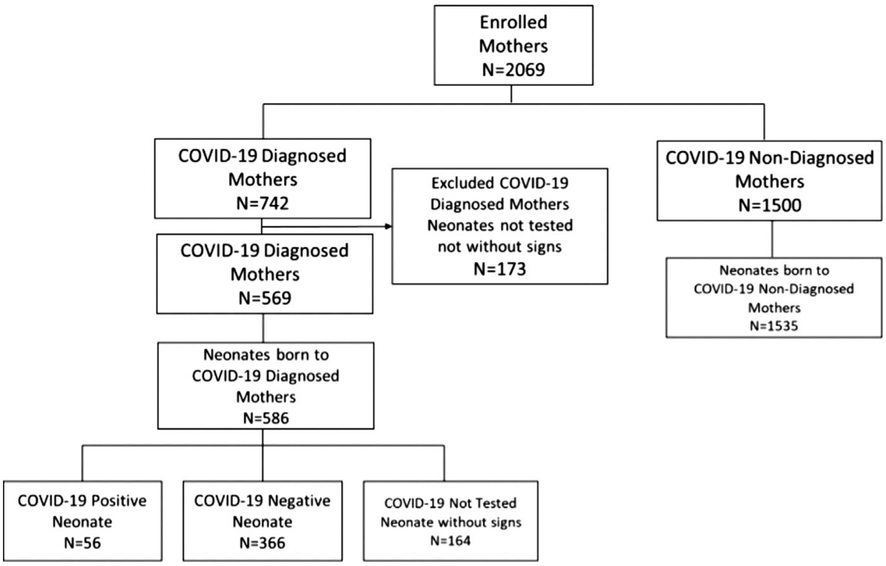
SUPPLEMENTAL FIGURE 2
Study enrollment flowchart, INTERCOVID study



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SUPPLEMENTAL TABLE 1
Indications for delivery among neonates born by cesarean delivery to mothers with COVID-19 diagnosis in the INTERCOVID Study

Reason for cesarean delivery	Mother with COVID-19 diagnosis Neonate COVID-19 negative (n=177) n (%)	Mother with COVID-19 diagnosis Neonate COVID-19 positive (n=40) n (%)
Cesarean delivery	177 (48.5)	40 (71.4)[a]
Potentially COVID-19 related[b]	85 (48.6)	19 (47.5)
PIH	17 (9.7)	1 (2.5)
Preeclampsia	8 (4.6)	1 (2.5)
Eclampsia/HELLP	11 (6.3)	2 (5.0)
Fetal distress	37 (21.0)	10 (25.0)
PROM	15 (8.6)	2 (5.0)
SGA	20 (11.4)	6 (15.0)
Infection	10 (5.7)	1 (2.5)

HELLP, hemolysis, elevated liver enzymes and low platelets; *PIH*, pregnancy-induced hypertension; *PROM*, premature rupture of membranes; *SGA*, small for gestational age.

*$P \leq .01$.

[a] $P \leq .001$ compared with mothers with COVID-19 diagnosis, COVID-19—negative neonates; [b] Fetal distress, PIH, preeclampsia, eclampsia/HELLP, fetal distress, PROM, SGA, and infection.

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SUPPLEMENTAL TABLE 2
Odds ratios and 95% confidence intervals for neonates testing positive for COVID-19 (n=56) of mothers with COVID-19 diagnosis (n=422) in the INTERCOVID Study

Predictor[a]	Unadjusted OR (95% CI)	*P* value
Separate bivariate logistic models		
Cesarean delivery	2.7 (1.4—4.9)	.002
Weeks from maternal positive test to delivery	1.1 (1.0—1.2)	.01
Gestational weeks at maternal diagnosis	0.90 (0.85—0.96)	.002
Immediate skin-to-skin contact	0.4 (0.2—0.8)	.008
Single multivariable logistic model	**Adjusted OR (95% CI)**	
Cesarean delivery	2.4 (1.2—4.7)	.01
Weeks from maternal positive test to delivery	1.1 (1.0—1.2)	.007
Immediate skin-to-skin contact	0.5 (0.2—1.0)	.05

CI, confidence interval; *OR*, odds ratio.

[a] Predictors adjusted for other predictors in multivariable model.

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SUPPLEMENTAL TABLE 3

Odds ratios and 95% confidence intervals for neonates testing positive for COVID-19 of mothers with COVID-19 diagnosis in the INTERCOVID Study

Days between diagnosis and delivery	N positive	Unadjusted OR (95% CI)	*P* value	Adjusted[a] OR (95% CI)	*P* value	% tested	% positive
>1 d	26	1.0 (0.6—1.8)	.97	0.9 (0.5—1.6)	.72	49.2	13.9
>3 d	20	1.2 (0.7—2.2)	.55	1.1 (0.6—2.1)	.69	43.9	15.1
>5 d	19	1.6 (0.9—3.0)	.11	1.6 (0.9—3.0)	.13	40.2	18.4
>7 d	18	1.9 (1.0—3.6)	.04	2.0 (1.0—3.7)	.04	38.1	20.2
>14 d	15	4.0 (2.0—8.0)	<.001	4.5 (2.2—9.4)	<.001	26.4	33.3

CI, confidence interval; *OR*, odds ratio.

[a] Adjusted for cesarean delivery.

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SUPPLEMENTAL TABLE 4

Characteristics and outcomes of neonates born to mothers with a COVID-19 diagnosis stratified by time between diagnosis and delivery in the INTERCOVID Study

Characteristic	Neonate tested >24 h after delivery (n=106) n (%)	Neonate tested ≤24 h after delivery (n=316) n (%)	*P* value
Delivery outcomes			
Test positivity	16 (15.1)	40 (12.7)	.52
Cesarean delivery	58 (55.2)	159 (50.3)	.38
Gestational age at delivery	37.6 (2.6)	37.8 (3.0)	.40
5-min Apgar score	8.9 (1.5)	9.1 (1.2)	.36
Intrapartum distress	16 (15.1)	28 (8.9)	.07
Neonatal outcomes			
NICU admission	41 (38.7)	108 (34.7)	.46
NICU ≥7 d	23 (21.7)	41 (13.4)	.04
Any breastfeeding at discharge	78 (75.0)	252 (81.3)	.17
Breast milk, no breastfeeding	5 (5.8)	29 (9.8)	.26
Oral feeding, no breast milk	19 (22.1)	64 (21.6)	.91
Neurologic conditions	2 (1.9)	13 (4.1)	.28
Feeding problems	10 (9.4)	20 (6.3)	.28
Gastrointestinal conditions	4 (3.8)	7 (2.2)	.38
Anemia requiring transfusion	2 (1.9)	8 (2.6)	.70
Congenital malformation	2 (1.9)	10 (3.2)	.49
Any other serious conditions	5 (4.7)	11 (7.8)	.57
Fever	2 (1.9)	4 (1.3)	.65
Infections	20 (18.9)	22 (21.0)	.25
Antibiotics	14 (13.2)	56 (17.7)	.79
Respiratory conditions	18 (17.0)	68 (21.5)	.32
Respiratory support	24 (22.6)	60 (1.3)	.28
Death	0 (0.0)	4 (1.0)	.29
Newborn care form			
Immediate skin-to-skin contact	45 (43.7)	114 (36.8)	.21
Newborn isolated from mother	48 (46.6)	152 (48.7)	.71
Mother wore a mask	93 (90.3)	281 (90.1)	.95
Mother washed hands before touching the newborn	96 (95.1)	268 (86.7)	.02
Hospital policy of staff wearing mask and gloves	99 (96.1)	311 (99.7)	.004

NICU, neonatal intensive care unit.

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SUPPLEMENTAL TABLE 5

Adjusted[a] relative risks for neonatal COVID-19 test status and neonatal outcomes among neonates born to COVID-19–positive mothers in the INTERCOVID Study

Outcome	Neonate COVID-19 negative aRR (95% CI)	Neonate without signs not tested aRR (95% CI)	Neonate COVID-19 positive aRR (95% CI)
Any respiratory conditions	4.0 (1.7–9.4)	1.7 (0.6–4.6)	5.6 (2.3–13.8)
Respiratory support	2.7 (1.4–5.5)	1.1 (0.5–2.8)	4.1 (1.9–8.7)
Neurologic conditions	3.7 (0.6–24.5)	Not observed[b]	5.5 (0.8–41.0)
Feeding problems	16.2 (1.1–247.7)	3.4 (0.2–61.9)	27.7 (1.8–419.1)
Anemia requiring transfusion	1.3 (0.3–7.2)	Not observed[b]	Not observed[b]
Fever	0.9 (0.0–35,7)	Not observed[b]	10.2 (0.5–252.1)
Gastrointestinal conditions	2.6 (0.3–21.9)	Not observed[b]	13.3 (1.5–119.1)
Infections	6.5 (2.2–19.6)	2.2 (0.6–7.7)	7.7 (2.4–24.5)
Antibiotics	3.1 (1.4–7.1)	1.0 (0.3–3.2)	2.7 (1.0–7.2)
NICU ≥7 d	2.9 (1.1–7.8)	0.1 (0.0–1.2)	5.2 (1.8–15.1)

aRR, adjusted relative risk; *CI*, confidence interval; *NICU*, neonatal intensive care unit.

[a] The reference group were mothers without COVID-19 diagnosis, adjusted for maternal age, tobacco use, parity, history of pregnancy complications, and gestational age; [b] Relative risk not estimated, no cases.

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SUPPLEMENTAL TABLE 6

Unadjusted relative risks for neonatal COVID-19 test status and neonatal outcomes among neonates born to COVID-19–positive mothers[a] in the INTERCOVID Study

Outcome	N	Neonate COVID-19 negative Unadjusted RR (95% CI)	Neonate without signs not tested Unadjusted RR (95% CI)	Neonate COVID-19 positive Unadjusted RR (95% CI)
Any respiratory condition	2301	2.4 (1.8–3.2)	1.1 (0.6–1.6)	3.9 (2.4–6.1)
Respiratory support	2277	2.2 (1.7–2.9)	1.1 (0.7–1.9)	3.9 (2.5–6.1)
Neurologic conditions	2301	2.3 (1.1–4.8)	Not observed[b]	5.5 (1.9–15.6)
Feeding problems	2301	1.5 (0.9–2.5)	0.5 (0.2–1.5)	3.6 (1.8–7.0)
Anemia requiring transfusion	2274	4.7 (1.7–12.7)	Not observed[b]	3.4 (0.4–26.7)
Fever	2275	1.4 (0.2–11.5)	Not observed[b]	18.1 (4.5–73.1)
Gastrointestinal conditions	2301	1.1 (0.5–2.8)	Not observed[b]	6.2 (2.2–17.8)
Infections	2301	2.2 (1.6–2.9)	1.4 (0.9–2.2)	2.9 (1.7–5.0)
Antibiotics	2276	2.1 (1.5–2.9)	1.1 (0.6–2.0)	2.4 (1.3–4.5)
NICU ≥7 days	2261	3.1 (2.1–4.5)	0.6 (0.2–1.5)	6.0 (3.4–10.4)

CI, confidence interval; *NICU*, neonatal intensive care unit; *RR*, relative risk.

[a] The reference group were mothers without COVID-19 diagnosis; [b] Relative risk not estimated, no cases.

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SUPPLEMENTAL TABLE 7

Unadjusted relative risks for neonatal COVID-19 test status and neonatal outcomes among neonates born to COVID-19—positive mothers[a] in the INTERCOVID Study

Outcome	N	Neonate COVID-19 negative Unadjusted RR (95% CI)	Neonate without signs not tested Unadjusted RR (95% CI)	Neonate COVID-19 positive Unadjusted RR (95% CI)
Any respiratory condition	707	2.8 (1.4—5.3)	1.2 (0.5—2.6)	4.3 (2.0—9.1)
Respiratory support	698	2.9 (1.5—5.6)	1.4 (0.6—3.2)	5.2 (2.5—11.1)
Neurologic conditions	707	2.2 (0.5—10.0)	Not observed[b]	4.0 (0.7—23.6)
Feeding problems	707	4.5 (1.1—19.0)	1.1 (0.2—7.4)	9.4 (2.0—43.6)
Anemia requiring transfusion	697	Not observed[b]	Not observed[b]	Not observed[b]
Fever	697	0.8 (0.1—12.6)	Not observed[b]	10.4 (1.1—100.2)
Gastrointestinal conditions	707	2.5 (0.3—20.2)	Not observed[b]	13.5 (1.5—119.0)
Infections	707	4.2 (1.8—9.4)	1.4 (0.5—3.9)	5.4 (2.1—13.9)
Antibiotics	697	3.3 (1.5—7.6)	1.2 (0.4—3.5)	3.5 (1.3—9.5)
NICU ≥7 d	687	2.1 (1.1—4.3)	0.2 (0.1—1.1)	4.3 (1.9—9.6)

CI, confidence interval; *NICU*, neonatal intensive care unit; *RR*, relative risk.

[a] The reference group were mothers without COVID-19 diagnosis, exposed mothers tested positive; [b] Relative risk not estimated, no cases.

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