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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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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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CONDENSATION

COVID-19 diagnosis in pregnancy and the postnatal period carries a substantial risk of neonatal morbidity and mortality, as compared with their not-exposed counterparts, with the most severe effects observed in test-positive neonates born to women with COVID-19 diagnosis.

SHORT TITLE

Association of prenatal exposure to maternal COVID-19 and perinatal care with neonatal outcome.

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.

What are the key findings?

COVID-19 diagnosis in pregnancy and the postnatal period carries a substantial risk of neonatal morbidity and mortality, as compared with their not-exposed counterparts, with the most severe effects observed in test-positive neonates born to women with COVID-19 diagnosis. Cesarean section was significantly associated with neonatal positivity. Vaginal delivery should be considered as the preferred mode of delivery even in symptomatic women, when obstetric and general health conditions allow it. Mother to child skin-to-skin contact, rooming-in and direct breastfeeding do not represent 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 study add to the already known?

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

Abstract

BACKGROUND The effect of COVID-19 in pregnancy on maternal outcomes and its association with preeclampsia and gestational diabetes has been reported; however, a detailed understanding of the effect 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 the 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, not-exposed 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 of COVID-19 and/or radiological pulmonary findings or 2 or more 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 section (52.8% compared to 38.5% for those without COVID-19 diagnosis, $p<0.01$) and pregnancy related complications such as hypertensive disorders of pregnancy and fetal distress, all with p-value < 0.001, compared to women without COVID-19 diagnosis. Maternal diagnosis of COVID-19 carried an increased rate of preterm birth ($p \leq 0.001$) and lower neonatal weight ($p \leq 0.001$), 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 (OR, 4.5; 95% CI 2.2-9.4 for length of in-utero exposure > 14 days). Among neonates born to mothers with COVID-19 diagnosis, birth via cesarean section was a risk factor for them testing positive for COVID-19 (OR 2.4, 95% CI 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 Intensive Care Unit admission, fever, gastrointestinal and respiratory symptoms and death, even after adjusting for prematurity. Breastfeeding by mothers with COVID-19 diagnosis, as well as hospital neonatal care practices including immediate skin-to-skin contact and rooming-in, were not associated with an increased risk of newborn positivity.

CONCLUSIONS In this multinational cohort study, COVID-19 in pregnancy was associated with increased maternal and neonatal complications. Cesarean section 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 did not represent risk factors for newborn COVID-19 diagnosis, thus well-established best practices can be continued among women with COVID-19 diagnosis.

Keywords

COVID-19, SARS-Cov-2, pregnancy, newborn, neonate, preterm birth, perinatal practices, breastfeeding, skin-to-skin, rooming-in, morbidity, mortality, risk ratio, small for gestational age, cesaean section, respiratory symptoms, NICU admission, neonatal outcomes, neurological outcome, intrauterine growth restriction, birthweight, infections, respiratory support, feeding problems, hospital stay, SARS-CoV-2 exposure, cohort, multicenter study, preeclampsia, risk ratio.

INTRODUCTION

The COVID-19 pandemic is likely to continue to affect large numbers of pregnant individuals and their offspring. While 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.

While increasing data are available relating 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 the neonatal period causes a 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) [9,10], 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 INTERGROWTH-21st Consortium initiated INTERCOVID, a prospective, multi-country, multi-center, 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 [11-14] and the association with preeclampsia [15] and gestational diabetes [16] have recently been reported. The present report focuses on the impact of COVID-19 on neonatal outcomes and the role of the mode of delivery, breastfeeding and early neonatal care practices on the risk of mother-to-child transmission [17-19].

MATERIALS AND METHODS

Study design

From 2 March 2020 to 18 March 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, UK, and the US). 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 old, at any stage of pregnancy or at delivery, with a COVID-19 diagnosis based on: a) laboratory confirmation of SARS-CoV-2 infection by RT-PCR (n=687); b) ≥2 predefined COVID-19 symptoms or signs, without laboratory confirmation (n=55). When a woman with COVID-19 diagnosis was identified antenatally, two immediately concomitant women without COVID-19 diagnosis aged ≥18 years old of similar gestational age (±2 weeks), receiving standard antenatal care, were enrolled that day in order to create an unbiased sample of all pregnant individuals without COVID-19 diagnosis in these institutions. If not possible or if the women without COVID-19 diagnosis were lost to follow-up, we enrolled two 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 employed when a woman with COVID-19 diagnosis was identified at hospital admission and delivery was likely during that admission. As a quality check, we sought confirmation, from a bi-weekly random 10% sample, that the two women without COVID-19 were appropriately chosen; we excluded five women with COVID-19 diagnosis and the corresponding women without COVID-19 diagnosis where such confirmation was missing [12].

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, singleton and multiple pregnancies were included, even those with congenital anomalies. In keeping with reporting requirements during the pandemic, we excluded mothers/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/exemption of 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 [12].

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.

Maternal and pregnancy history and delivery mode were collected together with indication for caesarean section, newborn outcomes, and feeding practices with standardized forms as used in the INTERGROWTH-21st Project [20]. In addition, we recorded detailed data on each mother's health and condition at admission, perinatal management, and in-hospital practices (e.g., skin-to-skin contact, isolation from the neonate, and the practice by mother and hospital staff of using masks and hand washing). We also recorded information regarding the timing and results of SARS-CoV-2 testing and COVID-19-related symptoms for mother and neonate.

Gestational age estimation was based on ultrasound measurement of fetal crown-rump length (<14 weeks' gestation) [21] or, if early ultrasound dating was not carried out, the "best obstetric" 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 cut off to study the risk in different populations (i.e., women still infectious during labour versus women most probably not-infectious during labour) as the horizontal infectiousness of patients with symptoms or a positive test more than 10 days earlier appears very low [22,23]. The maternal symptoms severity score was defined as a continuous variable made up of the sum of pre-set 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 section, those indications were grouped into those potentially COVID-19-related *vs* others. We included in the potentially COVID-19-related indications hypertensive disorders of pregnancy [15], fetal distress, fetal growth restriction, suspected small for gestational age (SGA) or fetal growth restriction [10], premature rupture of membranes (PROM), and infections. SGA was defined as being born with weight below the 10th percentile based on INTERGROWTH-21th International Standards for newborn weight [24].

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. Neonatal health outcomes, diagnostics and treatments were collected in detail and then presented as categories: 1) Neurological problems including seizures, hydrocephalus, neurological disorders, any hypoxic-ischaemic encephalopathy and grade 3 or 4 per Papile criteria periventricular haemorrhage/Leukomalacia; 2) Gastrointestinal conditions including no enteral feeding for > 24 hours, necrotising enterocolitis, stoppage of enteral feeding for more than three consecutive days, gastro-esophago-pharyngeal reflux, persistent vomiting, and diarrhoea; 3) Infections including sepsis, hypotension requiring inotropic-steroids and pneumonia/acute respiratory infections; 4) Respiratory conditions including pneumonia/bronchiolitis, apnea of prematurity, bronchopulmonary dysplasia (BPD) and corticosteroids for BPD.

Detailed data regarding feeding were recorded and included: the type of feeding, i.e., any breastfeeding (defined as exclusive or partial breastfeeding) and no breastfeeding (defined as exclusive formula or only parenteral nutrition); mode of feeding, i.e., direct breastfeeding, bottle feeding, or tube feeding. Also, 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.

Due to 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 list of the Study Documents that can be accessed on the INTERCOVID website [20].While most centers tested all newborns from mothers with COVID-19 diagnosis, a few tested only newborns with clinical signs, e.g. fever, respiratory distress or need for respiratory support. The analysis is therefore conducted on three 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 three groups of neonates. We used negative binomial models to calculate relative risks for neonatal outcomes among the three 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 [25]: maternal age, tobacco use, parity, history of pregnancy complications and gestational age. To complement the crude, unadjusted analysis, we explored logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI) 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 (Supplementary Table 3).

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 section 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, as a 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: a) laboratory confirmation of SARS-CoV-2 infection by RT-PCR (n=687); b) ≥2 predefined COVID-19 symptoms or signs, without laboratory confirmation (n=55). Mother/newborn dyads in which the neonate was not tested for COVID were excluded (n=180 neonates and 173 mothers).

We therefore included in this analysis 569 women with, and 1500 women without COVID 19 diagnosis. Since 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 as 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, the former group subdivided into those with neonates who tested positive or negative for COVID-19, and those without clinical signs who were not tested. Women with COVID-19 diagnosis had a higher rate of hypertensive disorders of pregnancy and pregnancy induced hypertension, as well as higher occurrence of gestational diabetes, previous neonatal death, previous preterm birth, and previous low birth weight child compared to women without COVID-19 diagnosis. Compared to pregnant individuals without COVID-19 diagnosis, pregnant persons with COVID-19 diagnosis had higher incidence of cesarean section, preterm birth, medically-

indicated preterm birth and related prophylactic antenatal corticosteroid therapy given for fetal lung maturation, all with $p < 0.01$, reflecting higher rates of pregnancy complications in this group. For all these variables, women with COVID-19 diagnosis had higher rates (p-value < 0.01) compared to women without COVID-19 diagnosis.

Women with COVID-19 diagnosis had a cesarean section rate (see table 1) of 52.8% compared to 38.5% for those without COVID-19 diagnosis ($p<0.01$). Among women with COVID-19 diagnosis, those with neonates that tested positive for COVID -19 had a cesarean section rate of 69.8% compared to 46.9% for those with neonates who tested negative ($p<0.01$). The reason for cesarean section did not significantly differ between groups, either individually or when grouped by COVID-19-related indications *vs* any other indications (see Supplemental Table 1). In a multivariable logistic regression analysis (see Supplemental Table 2), including time of exposure and immediate mother/newborn skin-to-skin contact, birth via cesarean section was statistically significantly associated with neonates testing positive for COVID-19 (aOR 2.4, 95% CI 1.2-4.7).

Moreover, we investigated if caesarean was independently associated with neonatal positivity and found no interaction between direct breast feeding and cesarean section (p-interaction = 0.93). Also the interaction term between skin to skin contact and cesarean section is marginally significant (p-interaction = 0.17). With skin to skin contact and the interaction between skin to skin and cesarean in the model, the odds ratio for neonate testing positive with cesarean section increases to 3.4 (1.4, 8.2), but the confidence intervals are much wider.

As presented in Table 1, fetal distress was lowest in neonates of women without COVID-19 diagnosis, higher among COVID-19 test- negative neonates of women with COVID-19 diagnosis, and highest among COVID-19 test 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. Amongst COVID-19 test-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 test-negative neonates (13.3 days versus 6.4 days, p=0.007) while the gestational age at diagnosis was significantly lower (35.3 weeks versus 37 weeks, p=0.002).

Figure 1 shows the ORs and 95% CIs for the COVID-19 test-positive neonates by the time elapsed between maternal diagnosis and delivery, adjusted for cesarean section. The aORs increase with the time between diagnosis and delivery, particularly after 7 days (aOR 2.0, 95% CI 1-3.7, p=0.04) and 14 days of exposure (aOR 4.5, 95% CI 2.2-9.4, p <0.001) (see Supplemental Table 3).

As shown in Table 2, we did not observe any significant differences regarding the severity and number of maternal symptoms across the three neonatal groups with mothers with COVID-19 diagnosis. Those test-positive neonates born to a woman with COVID-19 diagnosis had, on average, a gestational age at birth more than one week less than those neonates born to a woman without COVID-19 diagnosis (Table 2). Thus, birth weight, length and head circumference were, on average, lower among test-positive neonates born to women with a COVID-19 diagnosis than among those whose mothers without COVID-19 diagnosis. The rates of fetal distress in labour, NICU admission and early neonatal complications and morbidities among test-positive newborns of women with COVID-19 diagnosis were also higher than in those from mothers without COVID-19 diagnosis. NICU admission and early neonatal complications were also higher in test-negative newborns born to women with COVID-19 diagnosis, compared to women without COVID-19 diagnosis (Table 2).

Table 3 shows outcomes up to hospital discharge of test-negative, test-positive and not-tested neonates of women with COVID-19 diagnosis. A NICU stay longer than 7 days occurred significantly more frequently in test-positive than negative neonates. The proportion of any breastfeeding did not differ significantly between those who tested negative *vs* positive. However, a higher proportion who breastfed, both during hospital stay and discharge, was observed in not-tested neonates, in whom the rate of respiratory problems and infections was significantly lower than in test-negative neonates of women with COVID-19 diagnosis. In contrast, test-

positive neonates showed a significantly higher rate of complications such as fever, infections, respiratory problems or need for respiratory support compared to test-negative neonates. (Table 3)

Table 4 shows the increased relative risks for most neonatal outcomes comparing neonates born to a mother with COVID-19 diagnosis, to those born to a mother 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, CI 95% 2.2-5.3), neurological (OR 4.9, CI 95% 1.7-14.1) and gastrointestinal (OR 5.9, CI 95% 2.1-16.6) signs and the need for a NICU stay longer than 7 days (OR 5.4, CI 95% 3.2-9.1) among test-positive neonates compared to those with a mother without COVID-19 diagnosis. The results were similar, although the confidence intervals were wider, when we restricted this analysis only to mothers who tested positive for COVID-19 (Supplemental Table 5).

Table 5 provides data regarding care practices for the neonates of mothers with COVID-19 diagnosis. Immediate skin-to-skin contact was lower in test-positive than in test-negative neonates. Rooming-in with the mother; mother and hospital staff practices of wearing masks and washing their hands before touching the neonate, and the proportion of neonates who received breast milk did not differ. We specifically explored the association between feeding human milk regimens and neonatal COVID-19 test positivity and the risk of transmission of SARS-CoV-2 by breastfeeding, as compared to feeding expressed human milk. Any breastfeeding compared to exclusive formula or no oral feeding was not associated with neonatal test positivity. We did not find any differences in the risk of being test-positive between neonates who received direct breastfeeding and those receiving donor milk or extracted mother's breast milk administrated 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 [12]. Here, we concentrate on the role 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 association between *in utero* exposure, type of delivery and the neonatal risk of testing positive for COVID-19, as well as 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 section was significantly associated with neonatal COVID-19 test positivity. Mother to child skin-to-skin contact, rooming-in and direct breastfeeding do not represent 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 neonate 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 test-positive neonates of women with COVID-19 diagnosis, compared to 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 for neonates who then tested positive at birth, compared with those who tested negative (35.3 weeks versus 37 weeks). However, the time between maternal diagnosis and delivery was significantly longer in test-positive compared to test-negative neonates (13.3 days versus 6.4 days) resulting

406 in a similar mean gestational age at birth.

407 The pathogenic mechanisms that could explain the correlation between the total time of exposure and risk of
408 neonatal positivity are yet to be elucidated [26]. In general, it is considered that vertical transmission with SARS-
409 CoV-2 does not occur prenatally. However, the fact that SARS-CoV-2's cellular receptor, the angiotensin
410 converting enzyme-2 receptor (ACE-2), has been detected in the placenta, albeit at a low level, raises the
411 possibility of transplacental transmission [27] in some rare cases. Once SARS-CoV-2 binds to the ACE-2
412 receptor, the Transmembrane protease serine 2 enzyme (TMPRSS2) is activated and allows the virus to pass
413 into the cell; TMPRSS2 is expressed after 24 weeks' gestation [28]. Conflicting data exist related to the extent of
414 co-expression [29,30]. Viraemia is also associated with vascular damage, including hypercoagulability and poor
415 vascular perfusion [31]; the resulting placental damage could facilitate such vertical transmission [26].

416 The cesarean section rate was significantly higher in women with, compared women without COVID-19
417 diagnosis, possibly because obstetricians adopted a more interventional approach to the affected women.
418 However, when we focused on women with COVID-19 alone, the cesarean section rate was still significantly
419 higher in the test-positive (71.4%) compared to negative (48.9%) neonates. Analysis of both cesarean section
420 COVID-19-related indications and the severity of maternal conditions did not show any differences between the
421 test-positive and negative neonates, which reinforces the independence of cesarean section in determining
422 neonatal positivity, as confirmed also by multivariable logistic analysis. There is no clear explanation for this
423 observation, although one interesting hypothesis is that neonates born by cesarean section have less immediate
424 contact with the mother with consequent less intake of colostrum, very rich in immunological protective factors
425 [32], which would increase the risk of SARS-CoV-2 infection. At present these exploratory data do not support a
426 recommendation for cesarean section in mothers with COVID-19 diagnosis.

427 Another important finding was that breastfeeding in mothers with COVID-19 diagnosis was not associated with
428 an increased risk for neonatal test positivity. Therefore, given the additional well-known benefits of the

mother's own milk on neonatal health, we strongly recommend that all measures to promote, protect and sustain breastfeeding should be maintained in mothers with COVID-19 diagnosis, as indicated by WHO and CDC guidelines [33,34]. 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 message about the commitment to breastfeeding in our populations and allowed us to have a good number of breastfed newborns in this study.

Finally, the data we collected on neonatal care practices showed that immediate skin-to-skin contact and rooming-in did not increase the risk of neonatal test 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 kept the neonate isolated from mothers with COVID-19 diagnosis, especially early in the pandemic [35,36]. Our data show that these are unnecessary practices and can deprive the mother and her neonate of the well-recognised beneficial effects of early contact such as closer bonding, early initiation and continuation of breastfeeding, and reduced infections [37].

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 recognise 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 gives even more strength to the differences identified between the groups.

We acknowledge a risk of ascertainment bias in reporting maternal and neonatal morbidity as the newborns of women with COVID-19 diagnosis compared to newborns of women without COVID-19 diagnosis, may have

been more strictly monitored and adverse events noted more rigorously. However, this limitation would not explain differences in the outcomes of test-positive compared to test-negative neonates all from the homogenous population of mothers with COVID-19 diagnosis. Another limitation is that, due to 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 [12,38].

Conclusions

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

Cesarean section 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 obstetric and general health conditions allow it. Mother to child skin-to-skin contact, rooming-in and direct breastfeeding do not represent risk factors for neonatal test positivity; thus, well-established best evidence-based practices can be continued among women withCOVID-19 diagnosis.

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published data. The Principal Investigators at each study site implemented the protocol at their respective institutions. CC, AW and RC led the quality control of data. FG, SD and RG wrote the manuscript with input from all co-authors. JV and ATP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors read the manuscript and made suggestions on its content. We thank all the contributing institutions and local researchers involved in the study. Appendix 1 contains their details as well as details of the study committees.

We are very grateful to the contributing institutions and local researchers involved in the study. The Appendix contains their details as well as details of the study committees.

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Table 1. Maternal COVID-19 diagnosis, neonatal COVID-19 test status and maternal baseline characteristics, INTERCOVID Study.

Maternal Characteristics	**Mothers without COVID-19 diagnosis (n=1500)** n (%) or Mean ± SD	**Mothers with COVID-19 diagnosis**			
		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, M±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 birth weight baby	104 (7.8)	45 (9.2)	25 (8.3)	15 (10.2)	5 (10.2)
Previous neonatal death	41 (3.1)	29 (5.8)*	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	125 (8.4)	66 (11.6)*	34 (9.7)	26 (16.1)	6 (11.3)
Maternal hypertension, preeclampsia or eclampsia	140 (9.4)	85 (15.0)*	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)*	43 (12.5)	14 (9.0)	9 (17.0)
Fetal distress	122 (8.2)	72 (12.7)*	49 (13.9)	14 (8.6)	9 (17.0)
Caesarean delivery	576 (38.5)	300 (52.8)*	165 (46.9)	98 (60.1)	37 (69.8)
Induced labour	336 (22.4)	123 (21.6)	82 (23.2)	33 (20.3)	8 (15.1)
Preterm birth	200 (13.4)	132 (23.2)**	83 (23.5)	32 (19.8)	17 (32.1)
Medically-indicated preterm birth	130 (8.7)	113 (19.9)**	70 (19.8)	26 (16.1)	17 (32.1)

† p≤0.05; * p≤0.01; ** p≤0.001 comparing neonates born to mother with COVID-19 diagnosis to neonates born to mother without COVID-19 diagnosis

Table 2. Maternal COVID-19 diagnosis, neonatal COVID-19 test status and early outcomes, INTERCOVID Study.

Neonatal characteristics	**Mother without COVID-19 diagnosis (n=1535)[a]** **n (%) or Mean ± SD**	**Mother with COVID-19 diagnosis**		
		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[#]	13.3 ± 23.8[#]
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*	35.3 ± 4.5*
Any maternal symptoms	NA	178 (48.6)	103 (62.8)	30 (53.6)
Maternal symptoms 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**
Testing within 24 hrs after birth	NA	195 (53.3)	NA	26 (46.4)
Testing within 48 hrs after birth	NA	276 (75.4)	NA	40 (71.4)
Male sex (%)	804 (52.8)	185 (50.6)	84 (51.5)	29 (52.7)
Birth weight (kg)[b]	3.09 ± 0.67	2.92 ± 0.69	2.96 ± 0.64	2.79 ± 0.84**
Birth length (cm)[b]	49.1 ± 3.9	48.4 ± 4.1	48.6 ± 5.1	47.2 ± 5.7*
Head circumference at birth (cm)[b]	34.1 ± 2.1	33.6 ± 2.2	34.1 ± 2.4	33.2 ± 2.7*
Birth weight 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)**
Meconium aspiration	8 (0.5)	5 (1.4)	0 (0.0)	2 (3.7)**
NICU admission (%)	164 (10.8)	121 (33.5)**	15 (9.4)	28 (50.0)**
Days in NICU (median & IQR)	5 (1-12)	4 (2-12)	3 (2-7)	7 (3-13)
Respiratory distress syndrome	74 (4.9)	37 (10.2)**	8 (5.0)	9 (16.1)**
Transient tachypnoea of newborn	39 (2.6)	25 (6.9)*	6 (3.7)	7 (12.5)**

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

[#] $p \leq 0.01$ comparing each category from mother with COVID-19 diagnosis (neonate without signs not tested and neonate positive) separately to negative neonates born to mother with COVID-19 diagnosis

† $p \leq 0.05$; * $p \leq 0.01$; ** $p \leq 0.001$ comparing each category from mother with COVID-19 diagnosis (neonate negative, neonate without signs not tested and neonate positive) separately to neonates born to mother without COVID-19 diagnosis.

[a] Numbers are different than Table 1 due to twin births.

[b] Mean ± SD

Table 3. – Neonatal outcomes of neonates born to mothers with, and without COVID-19 diagnosis, INTERCOVID Study.

Neonatal outcomes	**Mother without COVID-19 diagnosis (n=1535)[a] n (%)**	**Mother with COVID-19 diagnosis**		
		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)
Neurological conditions[a]	20 (1.3)	11 (3.0)	0 (0.0)†	4 (7.1)
Anaemia requiring transfusion	8 (0.5)	9 (2.5)	0 (0.0)†	1 (1.8)
Fever	6 (0.4)	2 (0.6)	0 (0.0)	4 (7.1)**
Gastrointestinal conditions[b]	22 (1.4)	6 (1.6)	0 (0.0)	5 (8.9)**
Infections[c]	123 (8.0)	63 (17.2)	18 (11.0)	13 (23.2)
Antibiotics	101 (6.6)	51 (14.1)	12 (7.5)†	9 (16.1)
Respiratory conditions[d]	121 (7.8)	69 (18.9)	14 (8.5)*	17 (30.4)†
Respiratory support ≤ 48 hours	74 (4.8)	29 (7.9)	12 (7.3)	10 (17.9)†
Respiratory support > 48 hours	45 (2.9)	33 (9.0)	2 (1.2)**	8 (14.2)
Any other serious condition	46 (3.0)	11 (3.0)	4 (2.5)	5 (8.9)†
NICU > 7 days	68 (4.5)	49 (13.7)	4 (2.5)**	15 (26.8)*
Death	23 (1.5)	1 (0.3)	4 (2.4)†	2 (3.6)*
Days at full oral feeding >1	100 (8.3)	55 (19.5)	14 (11.5)†	13 (25.5)
Any breastfeeding during hospitalization	1,083 (83.6)	254 (77.0)	130 (89.0)*	42 (79.3)
Any breastfeeding at discharge	1,329 (91.0)	288 (80.5)	138 (92.0)**	42 (75.0)

Abbreviations: NICU = neonatal intensive care unit; SD = standard deviation.

† p≤0.05; * p≤0.01; ** p≤0.001 compared to mother with COVID-19 diagnosis, child COVID-19 negative.

[a] Neurological problems includes seizures, hydrocephalus, neurological disorders, hypoxic-ischaemic encephalopathy, periventricular haemorrhage/leukomalacia.

[b] Gastrointestinal conditions include no enteral feeding for > 24 hours, necrotising enterocolitis, stoppage of enteral feeding for more than 3 consecutive days, gastro-oesophago-pharyngeal reflux, persistent vomiting, diarrhoea.

[c] Infections include sepsis, hypotension requiring inotropics/steroids, pneumonia/acute respiratory infections.

[d]Respiratory conditions include pneumonia/bronchiolitis, apnoea of prematurity, bronchopulmonary dysplasia, corticosteroids for BPD.

Table 4. Adjusted[a] relative risks for neonatal COVID-19 test status and neonatal outcomes among neonates born to mothers with COVID-19 diagnosis, 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)
Neurological 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)
Anaemia 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 ≥7 days	3.1 (2.1, 4.5)	0.4 (0.1, 1.2)	5.4 (3.2, 9.1)

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; NICU = neonatal intensive care unit.

[a] Reference group is mother 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.

Table 5. Characteristics of newborn care among neonates that tested negative and those that tested positive for COVID-19 among those born to mothers with COVID-19 diagnosis, INTERCOVID Study.

Characteristic	**Mother with COVID-19 diagnosis**	
	Neonate COVID-19 negative (n=358)	**Neonate COVID-19 positive (n=55)**
	n (%)	**n (%)**
Immediate skin-to-skin contact	147 (41.1)	12 (21.8)*
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)

† $p \leq 0.05$; * $p \leq 0.01$; ** $p \leq 0.001$ compared to neonate COVID-19 negative.

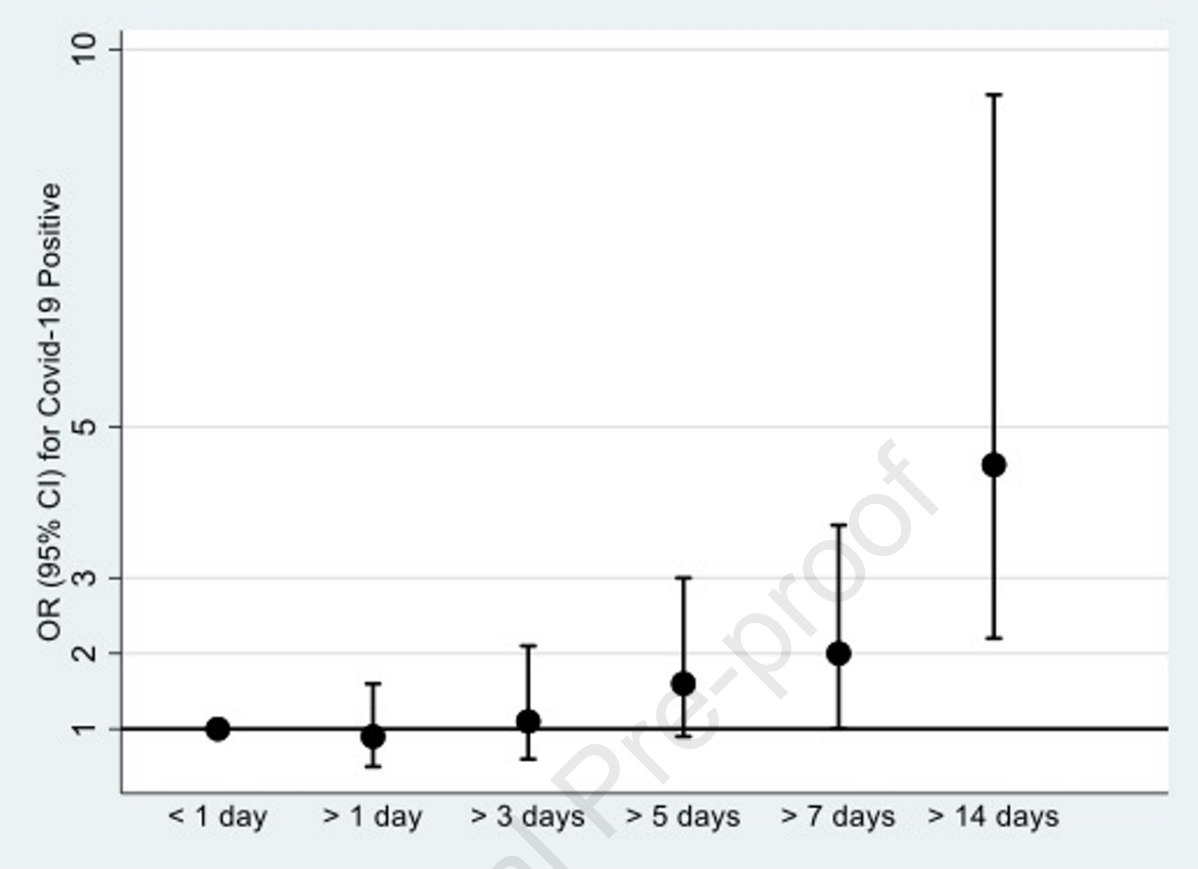
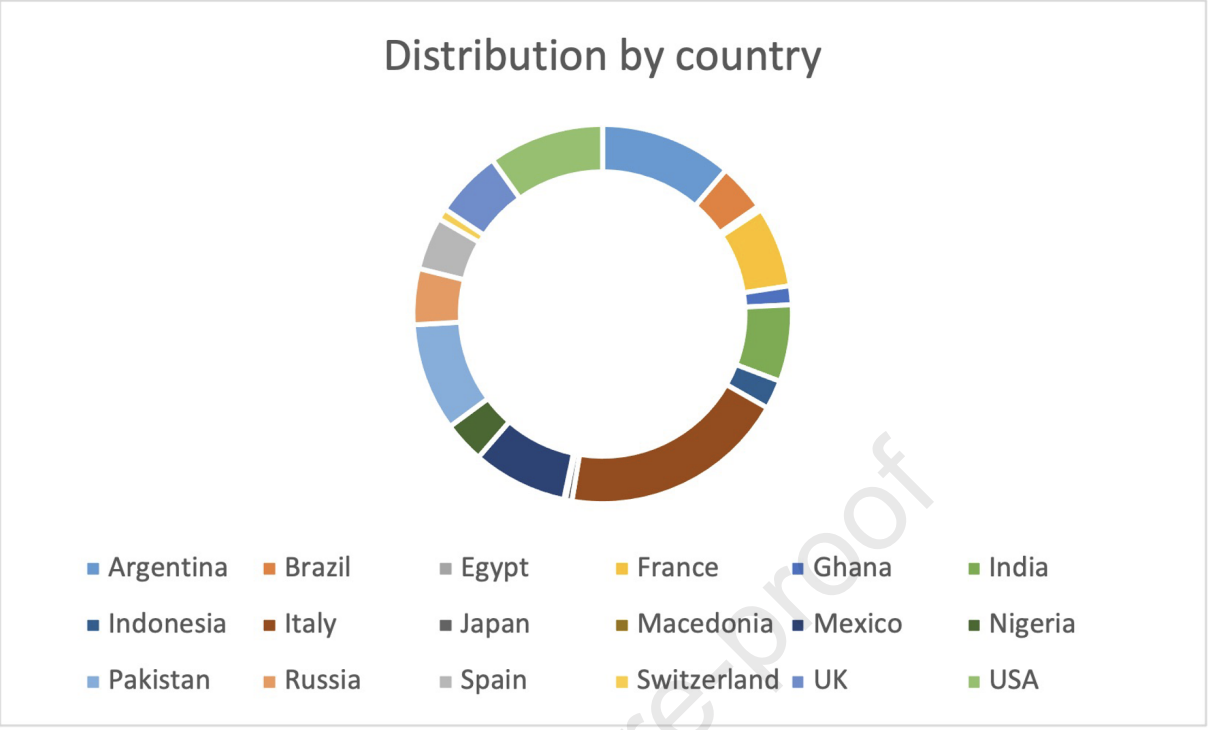


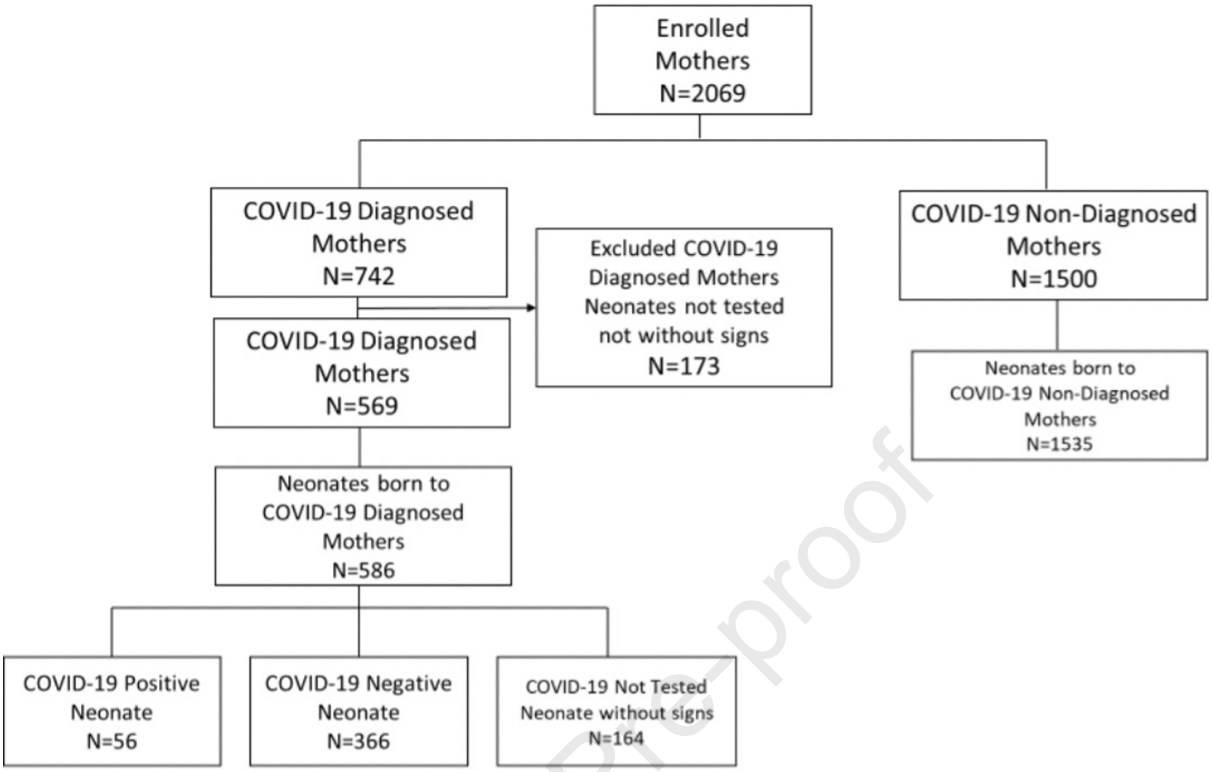
Figure 1. Adjusted[a] odds ratio and 95% confidence intervals for neonates testing COVID-19 positive by days between maternal COVID-19 diagnosis and delivery, INTERCOVID Study.

Abbreviations: CI = confidence interval; OR = odds ratio

[a] Adjusted for Caesarean section.



Supplemental Figure 1. Distribution of mothers with COVID-19 diagnosis by country, INTERCOVID Study.



Supplemental Figure 2. Study enrollment flowchart, INTERCOVID Study.