Covid-19 in pregnancy is associated with substantially higher maternal morbidity, mortality, preterm birth and severe neonatal complications: The INTERCOVID multinational study

Short title: Covid-19 in pregnancy is associated with maternal morbidity, mortality and newborn complications

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Key Points

Question

To what extent does Covid-19 in pregnancy alter the risks of adverse maternal and neonatal outcomes as compared to pregnant women without Covid-19?

Findings

In this prospective study, conducted in 18 countries, we assessed maternal and neonatal outcomes in women 'diagnosed' with Covid-19 at any stage of pregnancy or delivery compared to immediately concomitant, 'not-diagnosed' pregnant women from the same populations. 'Diagnosed' women were at increased risk of a composite maternal morbidity and mortality index (Relative Risk (RR) 1.54; 1.33 to 1.78), including a 1.6% risk of maternal mortality, which was 22 times higher than amongst 'not-diagnosed' women. Newborns of 'diagnosed' women had a significantly higher severe neonatal morbidity index (RR: 2.66; 1.69-4.18) and severe perinatal morbidity and mortality index (RR:2.14; 1.66-2.75).

Meaning

Our study indicates a consistent association between Covid-19 'diagnosed' pregnant women and higher rates of adverse outcomes, including maternal mortality, preeclampsia and preterm birth as compared with 'not-diagnosed' pregnant women.

Abstract

Importance: Detailed information about the effects of Covid-19 in pregnancy as compared with not-infected pregnant women is much needed.

Objectives: To evaluate the risks associated with Covid-19 in pregnancy on maternal and neonatal outcomes as compared with non-infected, concomitant pregnant women.

Design: Large, longitudinal, prospective, unmatched 'diagnosed'/'not-diagnosed' observational study assessing the association between Covid-19 in pregnancy and maternal and neonatal outcomes. Two consecutive 'not-diagnosed' women were concomitantly enrolled immediately after each 'diagnosed' 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 until hospital discharge, using the standardized INTERGROWTH-21st protocols and electronic data management system.

Setting: 43 institutions in 18 countries (Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, UK and USA).

Participants: A total of 706 'diagnosed' and 1424 'not-diagnosed' pregnant women were enrolled.

Exposure: Covid-19 in pregnancy.

Main outcome measures: The primary outcome measures were indices of 'Maternal morbidity and mortality', 'Severe neonatal morbidity and mortality' and 'Severe perinatal morbidity and mortality'; the individual components of these indices were secondary outcomes. Models for the primary outcome measures were adjusted for country, month entering study, maternal age and past history of morbidity.

Results: ‘Diagnosed’ women were at higher risk for preeclampsia/eclampsia (RR:1.76; 1.27-2.43), severe infections (RR:3.38; 1.63-7.01), intensive care unit (ICU) admission (RR:5.04; 3.13-8.10), maternal mortality (RR: 22.3; 2.88-172), preterm birth (RR:1.59; 1.30-1.94), medically-indicated preterm birth (RR:1.97; 1.56-2.51), severe neonatal morbidity index (RR:2.66; 1.69-4.18) and severe perinatal morbidity and mortality index (RR:2.14; 1.66-2.75). Fever and shortness of breath for any duration was associated with increased risk of severe maternal and neonatal complications. Asymptomatic ‘diagnosed’ women remained at higher risk only for maternal morbidity and preeclampsia. Among test-positive women, 13% of neonates tested positive; Cesarean delivery, but not breastfeeding, increased the risk for neonatal test positivity.

Conclusions and relevance: Covid-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications, when pregnant women ‘diagnosed’ and ‘not-diagnosed’ with the disease were compared. The findings should alert clinicians and women to implement strictly all the recommended Covid-19 preventive measures.

Introduction

At the outset of the Covid-19 pandemic, the precise extent of the risks in pregnancy was uncertain, which was affecting mothers' mental health.[1,2] The lack of clarity arose because, in an early systematic review,[3] only four studies, that involved small numbers, compared outcomes between pregnant women with and without Covid-19.[4-7] The question is relevant because of the known deleterious effects of other coronavirus infections in pregnancy, e.g. SARS (severe acute respiratory syndrome) and MERS-CoV (Middle East respiratory syndrome coronavirus).[8] Therefore, the INTERGROWTH-21st Consortium conducted a prospective, longitudinal, observational study (INTERCOVID), involving 43 hospitals in 18 countries, to assess the association between Covid-19 and maternal and neonatal outcomes in 'diagnosed' pregnant women, as compared with concomitantly enrolled, 'not-diagnosed' pregnant women.

Methods

STUDY DESIGN

For 8 months from 2 March 2020, we enrolled women aged ≥18 at any stage of pregnancy or delivery with the diagnosis of Covid-19 during the present pregnancy ('diagnosed' group) based on: a) laboratory confirmation of Covid-19 and/or radiological pulmonary findings suggestive of Covid-19 [9] or b) ≥2 predefined Covid-19 symptoms. Two immediately concomitant pregnant women aged ≥18, without any of those diagnostic criteria ('not-diagnosed' group) were enrolled per 'diagnosed' case to create an unbiased sample of all 'not-diagnosed' pregnant women in these institutions.

When a 'diagnosed' woman was identified antenatally, two 'not-diagnosed' women of similar gestational age (±2 weeks), receiving standard antenatal care, were enrolled that day. If not possible, or if those 'not-diagnosed' women were lost to follow-up, we enrolled two 'not-diagnosed' women

who delivered immediately after the 'diagnosed' woman. The same selection strategy was employed when a 'diagnosed' woman was identified at hospital admission and delivery was likely during that admission. If a 'not-diagnosed' woman declined participation, the next woman was approached until two 'not-diagnosed' women were enrolled per 'diagnosed' case. We sought confirmation, from a bi-weekly random 10% sample, that the two 'not-diagnosed' women were appropriately chosen; we excluded five 'diagnosed' women and the corresponding 'not-diagnosed' women without such confirmation. Live and stillborn, singleton and multiple pregnancies were included, even those with congenital anomalies. However, in keeping with reporting requirements during the pandemic,[10] we excluded women/neonates from the final analysis if their data were already published in any comparative study with 'not-diagnosed' women.[5,11-21]

OUTCOMES

The primary outcomes,[22] were three unweighted indices: 1) *'Maternal morbidity and mortality index' (MMMI)*, including a) at least one of the following pregnancy-related morbidities: third trimester vaginal bleeding, pregnancy-induced hypertension, preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome, preterm labor, infections requiring antibiotics, or any other pregnancy-related conditions requiring treatment or referral, or b) maternal admission to the intensive care unit (ICU), or referral to a higher level of care, or c) death; 2) *'Severe neonatal morbidity index'* (SNMI) including at least one of the following severe complications: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus requiring treatment or surgery, intraventricular hemorrhage, necrotizing enterocolitis or retinopathy of prematurity diagnosed before hospital discharge; 3) *'Severe perinatal morbidity and mortality index' (SPMMI)* including a) fetal death, or b) at least one of the severe neonatal conditions listed above, or c) admission to the Neonatal Intensive Care Unit (NICU) for ≥7

days, or d) neonatal death before hospital discharge. Secondary outcomes were each individual component of the indices described above considered as separate conditions.

Gestational age estimation was based on ultrasound measurement of fetal crown-rump length (<14 weeks' gestation) against the international INTERGROWTH-21st standards[23] 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. Newborn weight, length and head circumference at birth were assessed against the international INTERGROWTH-21st standards.[24]

DATA MANAGEMENT AND STATISTICAL ANALYSIS

We used a centrally coordinated data management system developed for the INTERGROWTH-21st Project (MedSciNet, London, UK).[25] Associations between being 'diagnosed' and morbidity/mortality indices expressed as binary outcomes were assessed using Poisson models with a log link function and robust standard errors expressed as Relative Risk (RR) and 95% confidence interval (CI). Associations with number of days in ICU were assessed using negative binomial models with robust standard errors (expressed as an Incidence Rate Ratio (IRR) and 95% CI). We set statistical significance at $p<0.05$. Models for our primary outcomes were adjusted for country, month entering study, maternal age and a past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis). Models with preterm birth as an outcome were also adjusted for previous preterm birth. We plotted Kaplan-Meier curves with the percentage remaining pregnant by gestational age to compare the distributions between 'not-diagnosed' and 'diagnosed' women according to symptom status. We evaluated 'diagnosed' women for the primary and secondary outcomes using the 'not-diagnosed' women as the reference group. We further categorized 'diagnosed' women as asymptomatic or symptomatic, based on type and duration of symptoms, as

well as according to past maternal morbidity and normal or overweight to explore effect modification. We assessed the effect of neonates testing positive for SARS-CoV-2 infection. In separate sensitivity analyses, we adjusted for additional potential confounders, restricted the 'diagnosed' definition to mothers with a positive laboratory test, and excluded twins. We also performed separate meta-analyses for our primary outcomes of interest using the stratified results to estimate pooled effects and assess heterogeneity by country.

The Oxford Tropical Research Ethics Committee and all local ethics committees provided approved the study, which did not interfere with clinical management. Informed consent (oral or written) was obtained from study 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 principles and Good Clinical Practice guidelines. The study protocol, including the laboratory tests used, is available at https://intergrowth21.tghn.org/intercovid/.

Results

We enrolled 706 Covid-19 'diagnosed' women: 656 with laboratory/radiological confirmation and 50 with >2 symptoms without laboratory confirmation. Of those who tested positive - almost exclusively by real-time polymerase chain reaction (RT-PCR) - 40.8% were asymptomatic. We also enrolled 1424 Covid-19 'not-diagnosed' women (eFigure 1). The 'diagnosed' and 'not-diagnosed' groups had similar demographic characteristics. However, 48.6% 'diagnosed' compared to 40.2% 'not-diagnosed' women were overweight early in pregnancy. 'Diagnosed' women had a higher rate of recreational drug use but lower rate of smoking during the index pregnancy, higher rates of previous preterm birth, stillbirth, neonatal death and pre-existing medical conditions (eTable 1).

During the index pregnancy, Covid-19 'diagnosed' women had higher rates of pregnancy-induced hypertension (RR=1.46; CI 1.05-2.02), preeclampsia/eclampsia (RR=1.76; CI 1.27-2.43), and infections

requiring antibiotics (RR=3.38; CI 1.63-7.01), and greater risk of admission to ICU/high-dependency unit (RR=5.04; CI 3.13-8.10) and referral to a higher level of care (RR=6.07; CI 1.23-30.01). Among all ICU admissions, 'diagnosed' women stayed 3.73 (CI 2.37-5.86) days longer than 'not-diagnosed' women (Table 1).

Eleven 'diagnosed' women died (maternal mortality ratio = 159/10,000 births). Of these, four had severe preeclampsia (one superimposed on chronic hypertension and one associated with cardiomyopathy); three of these four women had respiratory failure that required mechanical ventilation and the fourth died from a pulmonary embolism. Five women had worsening respiratory failure antenatally, two of whom underwent Cesarean section and, despite intensive respiratory support, died later. The remaining two women developed fever, cough and breathlessness within 7 days of an uneventful delivery and died shortly after despite ICU care. In the 'not-diagnosed' group, there was one death due to pre-existing liver malignancy and cirrhosis. Thus, the 'diagnosed' women were 22 times more likely to die (RR=22.3; CI 2.88-172), although the confidence intervals were wide due to the small numbers (Table 1).

Overall, 'diagnosed' women had a lower rate of spontaneous initiation of labor but higher Cesarean section rate, reflecting the higher rates of pregnancy complications in this group. They also had higher RR's for preterm birth and fetal distress of 1.59 (CI 1.30-1.94) and 1.70 (CI 1.06-2.75), respectively. Overall, 83% of preterm births in 'diagnosed' women were medically-indicated; hence, the increased risk in this group (RR=1.97; CI 1.56-2.51) (Table 1). The leading indications for preterm delivery among 'diagnosed' women were preeclampsia/eclampsia/HELLP (24.7%), SGA (15.5%) and fetal distress (13.2%). The proportions of spontaneous preterm birth were similar. 'Diagnosed' women had a higher low birth weight rate (RR=1.58; CI 1.29-1.94). The rates of pre-labor rupture of membranes were similar in both groups (Table 1). Fully adjusting models of our primary outcomes for

all planned variables, reduced the sample size due to missing data, but affected the results minimally (eTable 2).

'Diagnosed' women delivered earlier than those 'not-diagnosed' after approximately 30 weeks' gestation, with the greatest difference <37 weeks' gestation. Figure 1 illustrates the probability of remaining pregnant after 25 weeks' gestation for the 'diagnosed' women, stratified into those with and without symptoms. Using the log-rank test for trend of survivor curves, we observed a significant downwards trend in the gestational age distributions that progressed from 'not-diagnosed', to 'diagnosed-asymptomatic', to 'diagnosed-symptomatic' ($p<0.001$ for this trend) (Figure 1). In regression models, the gestational age at delivery was 0.6 weeks shorter (CI -0.9, -0.3) in all 'diagnosed' women and 0.8 weeks shorter (CI -1.2, -0.5) in symptomatic 'diagnosed' women than in 'not-diagnosed' women.

The risk of the SNMI among neonates of 'diagnosed' women was significantly higher (RR=2.66; CI 1.69-4.18) than in those of 'not-diagnosed' women. The risk of the SPMMI was over twice as high in the 'diagnosed' group (RR=2.14; CI 1.66-2.75) (Table 1).

A total of 416 neonates, born to 'diagnosed' women were tested for SARS-CoV-2 (57.1% of the total 'diagnosed' mother/neonate dyads) – 51.5% in the first 24h after birth and 84.8% within the first 48h. Of these, 54 (12.9%) tested positive. Among test-positive women with test-positive neonates, the Cesarean section rate was 72.2%; that among test-positive women with test-negative neonates was 47.9%. The rate in the 'not-diagnosed' women was 39.4%.

In regression models, exploring factors associated with neonatal SARS-CoV-2 positivity, that included gestational age at delivery, Cesarean delivery, NICU stay ≥7 days and exclusive breastfeeding at discharge, only Cesarean delivery was independently associated with the risk of a test-positive neonate (RR=2.15; CI 1.18-3.91). Reassuringly, there was no association between exclusive

breastfeeding and neonatal test positivity (RR=1.10; CI 0.66-1.85).

eTable 3 shows the type, number and prevalence of symptoms reported. Overall, the presence of any symptoms increased the risk of adverse outcomes as compared with the 'not-diagnosed' group. Although 'diagnosed' but asymptomatic women had limited risk for most outcomes, there was still an association between the disease and preeclampsia (RR=1.63; CI 1.01-2.63). The presence of fever and shortness of breath, separately or in combination with any symptom cluster, markedly increased the risk of the three summary indices, as well as preterm birth (Table 2).

Having shortness of breath, chest pain and cough with fever was associated with a substantial increase in the risk for severe maternal and neonatal conditions, and preterm birth. However, it appears that a longer exposure to symptoms is needed to increase the risk for preeclampsia, e.g., 5-10 days of respiratory symptoms (RR=2.43; CI 1.29-4.58) (eTable 4).

Among those with no pre-pregnancy morbidities, and those not overweight at their first antenatal visit, 'diagnosed' women were still at increased risk of these complications compared to 'not-diagnosed' women. However, for maternal outcomes, those 'diagnosed' women with pre-pregnancy morbidities had the highest risk in the index pregnancy, suggesting that past morbidities modify the effect of Covid-19 exposure, especially for preeclampsia/eclampsia (RR=3.29; CI 2.03-5.33) (Table 3). Women who were overweight at the first antenatal visit and subsequently became 'diagnosed' had the highest risk for the MMMI (RR=1.81; CI 1.48-2.21), SNMI (RR=4.15; CI 2.15-8.01), SPMMI and preeclampsia/eclampsia (RR=2.62; CI 1.57-4.36) suggesting that overweight status modifies the effect of Covid-19 exposure (Table 3).

We also compared the risk for severe neonatal complications in test-positive and negative neonates of 'diagnosed' and 'not-diagnosed' women, the latter as a reference group. The risks for the SNMI, SPMMI and NICU stay ≥7 days were increased in the test-negative neonates of 'diagnosed' women.

However, the test-positive neonates of 'diagnosed' women had considerably higher risk for the SPMMI and, as expected, a large increased risk for ≥7-day NICU stay (Table 4).

In separate sensitivity analyses, adjusting for additional confounders (marital status, overweight, smoking and drug use during pregnancy), restricting 'diagnosed' mothers to laboratory confirmed positive and excluding twins, we found that relative risks for Covid-19 associated maternal and neonatal morbidities were similar to our main results (eTable 2). Furthermore, we treated each country (all hospitals in a country pooled) as if they were separate studies in a meta-analysis. The pooled estimated RR's (95% CI) were practically identical to the unadjusted and adjusted estimations, except for the SNMI, which was increased from the unadjusted RR 2.69; CI 1.72-4.20 to 2.91; CI 1.76-4.74. As expected, considering the variability of underlying populations and care systems, we identified some heterogeneity of RR estimates across countries in the meta-analysis for the MMMI (p=0.02) and SPMMI (p=0.005), although there was no systematic pattern among the countries.

Discussion

We conducted a large-scale, prospective, multinational study to assess the symptoms and associations between Covid-19 in pregnancy and maternal and neonatal outcomes that included, to our knowledge for the first time, immediately concomitant, pregnant women 'not-diagnosed' with Covid-19 from the same populations, carefully enrolled to minimize selection bias.

We have demonstrated that the 'diagnosed' women, compared to those 'not-diagnosed', were at substantially increased risk of severe pregnancy complications, including preeclampsia/ eclampsia/HELLP syndrome, ICU admission or referral to higher level of care, and infections requiring antibiotics, as well as preterm birth and low birth weight. The risk of maternal mortality was 1.6%, i.e., 22 times higher in the 'diagnosed' group. These deaths were concentrated in institutions from less developed regions, implying that when comprehensive ICU services are not fully available, Covid-

19 in pregnancy can be lethal. Reassuringly, we also found that asymptomatic 'diagnosed' women had similar outcomes to 'not-diagnosed' women, except for preeclampsia.

Importantly, the 'diagnosed' women, already at high risk of both preeclampsia and Covid-19 because of pre-existing overweight, diabetes, hypertension, cardiac and chronic respiratory diseases,[26] had almost four times greater risk of developing preeclampsia/eclampsia, which could reflect the known association with these co-morbidities and/or the acute renal damage that can occur in Covid-19 patients.[27]

Our data support reports of an association between Covid-19 and higher rates of preeclampsia/ eclampsia/HELLP syndrome,[17,28] but it is still uncertain whether Covid-19 manifests in pregnancy with a preeclampsia-like syndrome, or infection with SARS-CoV-2 results in an increased risk for preeclampsia. Uncertainty persists because the placentas of women with Covid-19, compared to controls, show vascular changes consistent with preeclampsia,[29] but the state of systemic inflammation and hypercoagulability found in severely ill non-pregnant patients with Covid-19 is also a feature of preeclampsia.[30]

It is known that in non-pregnant patients, distinct sub-types may be predictive of clinical outcomes,[31] We found the presence of any Covid-19 symptoms increased morbidity and mortality. Specifically, severe pregnancy and neonatal complication rates were highest in women if fever and shortness of breath were present, reflecting systemic disease; their presence for 1-4 days was associated with severe maternal and neonatal complications. This observation should influence clinical care and referral strategies.

The risks of severe neonatal complications, including NICU stay for ≥7 days, as well as the summary index of 'Severe neonatal morbidity' and its individual components, were also substantially higher in the 'diagnosed' group. The increased neonatal risk remained after adjusting for previous preterm

birth and preterm birth in the index pregnancy; thus, a direct impact on the newborn from Covid-19 is likely.

Overall, our results were consistent across morbidities, and mostly at an RR near or greater than 2 for maternal and neonatal outcomes, with narrow CIs excluding unity, and above 3-4 in several estimates. Sensitivity and stratified analyses confirmed the observed results. They are probably conservative because overall 41% of 'diagnosed' women were asymptomatic, a sub-group with a low risk of complications. Hence, higher morbidity and mortality risk should be expected for the general pregnant population, especially in low to middle-income countries.

We found 12.1% of neonates born to test-positive women also tested positive, a higher figure than in a recent systematic review.[32] We speculate whether contamination at the time of Cesarean section was responsible, as the rate in this mother/neonate positive subgroup was 72.2%. Reassuringly, as SARS-CoV-2 has not been isolated from breast milk,[33] breastfeeding was not associated with any increase in the rate of test-positive neonates.

Our results mostly reflect Covid-19 diagnosed in the third trimester. Thus, women 'diagnosed', or whose pregnancy ended, earlier in pregnancy, are underrepresented either because our study was exclusively hospital-based or earlier infection may manifest with mild symptoms, which are either ignored or managed in primary care. Alternatively, most women might have avoided attending hospital until late in pregnancy or when in labor. Clearly, the effect of Covid-19 early in pregnancy needs urgently to be studied.

Our study has expected limitations. Ideally, we would have collected data prospectively from all pregnancies in the participating institutions, but this was impractical because of their large number of deliveries. There was a small risk of selection bias associated with the 'not-diagnosed' reference group, despite all efforts to ensure they represented an unbiased sample of the general non-infected

pregnant population. The selection of 'diagnosed' cases was affected by whether routine testing was conducted; awareness of Covid-19 symptoms particularly early in the pandemic, and the availability of test kits. Where universal testing in pregnancy has been introduced, RT-PCR positive rates are 0.5% to 14% in asymptomatic women.[34,35] Hence, our 'not-diagnosed' group may have included small numbers of asymptomatic infected women (a cross-over effect when 'not-diagnosed' women were enrolled antenatally), which would result in more conservative estimates by reducing the differences between groups. Finally, we acknowledge a risk of reporting bias relating to maternal and neonatal morbidity as 'diagnosed' women and their newborns may have been more carefully evaluated, tested and more events reported than in the 'not-diagnosed' sample. However, we are reassured that the results reflect a true increased risk because of our careful data monitoring and use of severe morbidity markers.

In summary, our study indicates that Covid-19 in pregnancy is associated with substantial risk of morbidity and mortality in mothers and their babies worldwide, as compared with their not-infected pregnant counterparts, especially if the women are symptomatic or have co-morbidities. There is an urgent need to follow up these mothers and infants because of possible long-term health effects, including long Covid.

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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.

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Table 1. Pregnancy complications, perinatal events and neonatal morbidities among Covid-19 'diagnosed' and 'not-diagnosed' women and their newborns.

	Covid-19 'diagnosed' (n=706)	Covid-19 'not-diagnosed' (n=1424)	Relative Risk or β coefficient
	N (%)	N (%)	(95% CI)
'Maternal morbidity and mortality' index[a]	225 (31.9)	296 (20.8)	1.54 (1.33, 1.78)[b]
Vaginal bleeding	44 (6.2)	87 (6.1)	1.02 (0.72, 1.46)
Pregnancy-induced hypertension	58 (8.2)	80 (5.6)	1.46 (1.05, 2.02)
Preeclampsia/eclampsia/HELLP	59 (8.4)	63 (4.4)	1.76 (1.27, 2.43)[b]
Hemoglobin <10g/dl at >27 weeks' gestation	130 (18.4)	228 (16.0)	1.15 (0.91, 1.45)
Preterm labor	52 (7.4)	88 (6.2)	1.20 (0.86, 1.68)
Infections requiring antibiotics	25 (3.6)	16 (1.1)	3.38 (1.63, 7.01)
Admitted to ICU	59 (8.4)	23 (1.6)	5.04 (3.13, 8.10)
Number of days in ICU (mean, SD)	7.3 ± 7.8	2.0 ± 1.7	3.73 (2.37, 5.86)[c]
Referred for higher dependency care	6 (0.9)	1 (0.1)	6.07 (1.23, 30.01)
Maternal death	11 (1.6)	1 (0.1)	22.26 (2.88, 172.11)
Fetal distress	87 (12.3)	120 (8.4)	1.70 (1.06, 2.75)[b]
Spontaneous initiation of labor	333 (47.2)	793 (55.7)	0.85 (0.77, 0.93)
Induced labor	157 (22.3)	320 (22.5)	0.99 (0.84, 1.18)
Cesarean section	346 (49.0)	547 (38.4)	1.28 (1.16, 1.40)[b]
Pre-labor rupture of membranes	114 (16.1)	262 (18.4)	0.87 (0.71, 1.07)
Gestational age at birth, weeks (mean, SD)	37.9 ± 3.3	38.5 ± 3.1	-0.61 (-0.90, -0.32)[d]
Preterm birth (<37 weeks' gestation)	159 (22.5)	194 (13.6)	1.59 (1.30, 1.94)[e]
Spontaneous preterm birth	27 (3.8)	66 (4.6)	0.81 (0.52, 1.27)
Medically-indicated preterm birth	133 (18.8)	127 (8.9)	1.97 (1.56, 2.51)[e]
Birth weight, kg (mean, SD)	2.96 ± 0.70	3.07 ± 0.68	-0.11 (-0.18, -0.04)[d]
Male sex	353 (50.0)	749 (52.6)	0.95 (0.87, 1.04)
Low birth weight (<2500g)	145 (20.5)	181 (12.7)	1.58 (1.29, 1.94)[b]
Small for gestational age (<10th centile)[f]	97 (13.7)	181 (12.7)	1.03 (0.81, 1.31)
Exclusive breastfeeding at discharge	378 (53.5)	953 (66.9)	0.80 (0.74, 0.87)
Any breastfeeding at discharge	588 (83.3)	1290 (90.6)	0.92 (0.88, 0.96)
'Severe neonatal morbidity index'[g]	44 (6.2)	33 (2.3)	2.66 (1.69, 4.18)[b]
'Severe perinatal morbidity and mortality index'[h]	120 (17.0)	113 (7.9)	2.14 (1.66, 2.75)[b]

Abbreviations: CI, confidence interval; HELLP, Hemolysis, elevated liver enzymes, low platelet count; ICU, intensive care unit.

[a]Maternal morbidity and mortality index includes at least one of the following complications during pregnancy: vaginal bleeding, pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP, preterm labor, or infections requiring antibiotics; or maternal death, admission to ICU, or referral for higher dependency care.

[b]Models adjusted for country, month entering study, maternal age and past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis).

[c]Incidence Rate Ratio and 95% CI.

[d]β and 95% CI

[e]Models for preterm birth adjusted for past history of preterm birth, country, month entering study, maternal age and past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis).

[f]Against the international INTERGROWTH-21st Newborn Size Standards.[20]

[g]Severe neonatal morbidity index includes at least one of the following morbidities: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, or retinopathy of prematurity.

[h]Severe perinatal morbidity and mortality index includes any of the morbidities listed in the Severe neonatal morbidity index; or intrauterine or neonatal death, or NICU stay ≥7 days.

Table 2. Adjusted[a] associations for maternal and perinatal outcomes among Covid-19 'diagnosed' and 'not-diagnosed' women according to symptom status.

		MMMI[b]		SNMI[c]		SPMMI[d]		Preterm birth[e]		Preeclampsia/ eclampsia/HELLP	
Symptoms	N (%)	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Covid-19 'not-diagnosed'	**1424 (66.9)**	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
Covid-19 'diagnosed', asymptomatic	288 (13.5)	1.24	(1.00, 1.54)	1.42	(0.65, 3.08)	1.08	(0.69, 1.69)	0.99	(0.72, 1.36)	1.63	(1.01, 2.63)
Covid-19 'diagnosed', any symptom	418 (19.6)	1.76	(1.49, 2.08)	3.45	(2.14, 5.56)	3.09	(2.36, 4.04)	2.10	(1.67, 2.62)	2.00	(1.34, 2.99)
Symptomatic with diarrhea/vomiting	48 (2.3)	1.36	(0.85, 2.19)	4.66	(1.93, 11.30)	2.79	(1.57, 4.95)	2.76	(1.77, 4.30)	0.48	(0.07, 3.81)
Symptomatic with fever	199 (9.3)	1.89	(1.54, 2.32)	4.34	(2.53, 7.43)	3.81	(2.81, 5.17)	2.39	(1.82, 3.13)	1.82	(1.08, 3.06)
Symptomatic with shortness of breath	89 (4.2)	2.46	(1.96, 3.08)	3.88	(1.78, 8.49)	3.86	(2.62, 5.67)	2.88	(2.12, 3.89)	2.72	(1.59, 4.64)
Symptomatic with fever *and* shortness of breath	45 (2.1)	2.56	(1.92, 3.40)	4.97	(2.11, 11.69)	5.09	(3.30, 7.86)	3.40	(2.38, 4.86)	2.22	(1.06, 4.64)

Abbreviations: RR, relative risk; CI, confidence interval; MMMI, Maternal morbidity and mortality index; SPMMI, Severe perinatal morbidity and mortality index; SNMI, Severe neonatal morbidity index.

[a]All models adjusted for country, month entering study, maternal age and past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis).

[b]Maternal morbidity and mortality index includes at least one of the following complications during pregnancy: vaginal bleeding, pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count), preterm labor, or infections requiring antibiotics; or maternal death, admission to intensive care unit, or referral for higher dependency care.

[c]Severe neonatal morbidity index includes at least one of the following morbidities: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, or retinopathy of prematurity.

[d]Severe perinatal morbidity and mortality index includes any of the morbidities listed in the Severe neonatal morbidity index; or intrauterine or neonatal death, or NICU stay ≥7 days.

[e]Models for preterm birth also adjusted for previous history of preterm birth.

Table 3. Adjusted[a] associations between pre-existing maternal morbidity[b] or being overweight pre-pregnancy and maternal and neonatal outcomes according to Covid-19 diagnosis.

	N (%)	MMMI[c] RR (95% CI)	SNMI[d] RR (95% CI)	SPMMI[e] RR (95% CI)	Preterm birth[f] RR (95% CI)	Preeclampsia/ eclampsia/HELLP RR (95% CI)
'not-diagnosed', no past morbidity	1179 (55.4)	Ref	Ref	Ref	Ref	Ref
'not-diagnosed', past morbidity	245 (11.5)	1.20 (0.92, 1.54)	3.04 (1.48, 6.28)	1.48 (0.95, 2.29)	1.73 (1.26, 2.39)	1.86 (1.11, 3.12)
'diagnosed', no past morbidity	547 (25.7)	1.57 (1.33, 1.85)	4.02 (2.39, 6.76)	2.35 (1.76, 3.13)	1.76 (1.40, 2.22)	1.88 (1.24, 2.86)
'diagnosed', past morbidity	159 (7.5)	1.71 (1.33, 2.20)	1.88 (0.74, 4.73)	2.29 (1.50, 3.51)	1.96 (1.41, 2.73)	3.29 (2.03, 5.33)
'not-diagnosed', normal weight	823 (40.3)	Ref	Ref	Ref	Ref	Ref
'not-diagnosed', overweight	554 (27.1)	1.01 (0.81, 1.24)	1.56 (0.76, 3.20)	1.14 (0.78, 1.67)	0.78 (0.59, 1.05)	1.37 (0.82, 2.30)
'diagnosed', normal weight	342 (16.8)	1.28 (1.03, 1.58)	2.07 (0.99, 4.31)	1.99 (1.38, 2.88)	1.42 (1.07, 1.90)	1.80 (1.06, 3.07)
'diagnosed', overweight	323 (15.8)	1.81 (1.48, 2.21)	4.15 (2.15, 8.01)	2.44 (1.72, 3.48)	1.43 (1.08, 1.85)	2.62 (1.57, 4.36)

Abbreviations: RR, relative risk; CI, confidence interval; MMMI, Maternal morbidity and mortality index; SNMI, Severe neonatal morbidity index; SPMMI, Severe perinatal morbidity and mortality index.

[a]All models adjusted for country, month entering study, maternal age and past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis).

[b]Pre-pregnancy maternal morbidities included at least one of the following: diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis.

[b]Maternal morbidity and mortality index includes at least one of the following complications during pregnancy: vaginal bleeding, pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count), preterm labor, or infections requiring antibiotics; or maternal death, admission to intensive care unit, or referral for higher dependency care.

[d]Severe neonatal morbidity index includes at least one of the following morbidities: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, or retinopathy of prematurity.

[e]Severe perinatal morbidity and mortality index includes any of the morbidities listed in the Severe neonatal morbidity index; or intrauterine or neonatal death, or NICU stay ≥7 days.

[f]Models for preterm birth also adjusted for previous history of preterm birth.

Table 4. Adjusted[a] associations between maternal and neonatal Covid-19 diagnosis with perinatal morbidity and mortality.

	N (%)	SNMI[b] RR (95% CI)	SPMMI[c] RR (95% CI)	NICU ≥7 days RR (95% CI)
'not-diagnosed' mother and neonate	1462 (66.7)	Ref	Ref	Ref
'diagnosed' mother but neonate not tested	313 (14.3)	1.40 (0.72, 2.70)	1.68 (1.20, 2.37)	1.02 (0.60, 1.83)
'diagnosed' mother but test-negative neonate	362 (16.5)	4.00 (2.29, 6.97)	2.31 (1.69, 3.17)	3.13 (2.10, 4.65)
'diagnosed' mother and test-positive neonate	54 (2.5)	4.13 (1.69, 10.08)	3.46 (2.13, 5.63)	6.03 (3.35, 10.86)

Abbreviations: RR, relative risk; CI, confidence interval; SNMI, Severe neonatal morbidity index; SPMMI, Severe perinatal morbidity and mortality index; NICU, neonatal intensive care unit.

[a]Models adjusted for country, month entering study, maternal age and past history of maternal morbidity (including diabetes, thyroid and other endocrine disorders, cardiac disease, hypertension, chronic respiratory disease, kidney disease, malaria, or tuberculosis).

[b]Severe neonatal morbidity index includes at least one of the following morbidities: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, or retinopathy of prematurity.

[c]Severe perinatal morbidity and mortality index includes any of the morbidities listed in the Severe neonatal morbidity index; or intrauterine or neonatal death, or NICU stay ≥7 days.

Figure 1. Gestational age at delivery among ‘diagnosed’ women with and without symptoms and ‘not-diagnosed’ women.

Figure legend

There were 1420 ‘not-diagnosed’ women (shown in blue). In the ‘diagnosed’ group, 417 women were symptomatic (green) and 288 women were asymptomatic (red). There was a significant trend ($p<0.001$) in shorter gestational age at delivery going from ‘not-diagnosed’, to asymptomatic ‘diagnosed’ to symptomatic ‘diagnosed’ (log-rank test for trend of survivor curves). Five women with missing data were excluded from the figure.