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SARS-CoV-2 infection by trimester of pregnancy and adverse perinatal outcomes: a Mexican retrospective cohort study

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ABSTRACT

Objective Conflicting evidence for the association between COVID-19 and adverse perinatal outcomes exists. This study examined the associations between maternal COVID-19 during pregnancy and adverse perinatal outcomes including preterm birth (PTB), low birth weight (LBW), small-for-gestational age (SGA), large-for-gestational age (LGA) and fetal death; as well as whether the associations differ by trimester of infection.

Design and setting The study used a retrospective Mexican birth cohort from the Instituto Mexicano del Seguro Social (IMSS), Mexico, between January 2020 and November 2021.

Participants We used the social security administrative dataset from IMSS that had COVID-19 information and linked it with the IMSS routine hospitalisation dataset, to identify deliveries in the study period with a test for SARS-CoV-2 during pregnancy.

Outcome measures PTB, LBW, SGA, LGA and fetal death. We used targeted maximum likelihood estimators, to quantify associations (risk ratio, RR) and CIs. We fit models for the overall COVID-19 sample, and separately for those with mild or severe disease, and by trimester of infection. Additionally, we investigated potential bias induced by missing non-tested pregnancies.

Results The overall sample comprised 17 340 singleton pregnancies, of which 30% tested positive. We found that those with mild COVID-19 had an RR of 0.89 (95% CI 0.80 to 0.99) for PTB and those with severe COVID-19 had an RR of 1.53 (95% CI 1.07 to 2.19) for LGA. COVID-19 in the first trimester was associated with fetal death, RR=2.36 (95% CI 1.04, 5.36). Results also demonstrate that missing non-tested pregnancies might induce bias in the associations.

Conclusions In the overall sample, there was no evidence of an association between COVID-19 and adverse perinatal outcomes. However, the findings suggest that severe COVID-19 may increase the risk of some perinatal outcomes, with the first trimester potentially being a high-risk period.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study provides evidence of the relationship between maternal COVID-19 during pregnancy and adverse perinatal outcomes in the Mexican population that resembles the Hispanic population in the USA.
⇒ It used individual data as well as area-level characteristics and found that severe COVID-19 may increase the risk of adverse perinatal outcomes.
⇒ COVID-19 in the first trimester could increase the risk of fetal death.
⇒ The study population was limited to women who received care from the Mexican Institute of Social Security. Thus, caution should be exercised in extrapolating the findings to the entire population of women giving birth in Mexico.

INTRODUCTION

Globally, about 15 million preterm births (PTB) and 21 million low birth weight (LBW) neonates are born annually, which are the leading causes of neonatal deaths.[1–3] The proportion of these outcomes in Latin America is between 9% and 12%, which is higher than the high-income countries but lower than South Asia and sub-Saharan Africa.[4] Whether COVID-19 exacerbated these outcomes, either directly by affecting maternal health during pregnancy or indirectly by limiting access to health services, remains unclear.

The evidence of association between COVID-19 and adverse perinatal outcomes is mixed, while some studies suggest associations, others do not.[5–14] Some retrospective studies have reported increased associations with PTB, reduced birth weight and small-for-gestational age (SGA) among mothers with severe or critical COVID-19, compared with pregnancies with mild, asymptomatic or no disease.[8 15 16] Prospective studies of relatively small but different populations yielded mixed results. One study reported almost a five-fold increase in the risk of fetal death among SARS-CoV-2 pregnancies, but no risk of PTB or reduced birth weight[17]; while

others reported higher proportions of PTB than usually observed in the general population.[18–23] However, several large studies including a national cohort did not find any association.[14 19 24 25] Two large reviews, comparing COVID-19 with non-COVID-19 pregnancies, reported positive associations with PTB and LBW.[26 27]

The severity and timing of COVID-19 (ie, disease early in pregnancy) may impact fetal growth because immature placentas are vulnerable to viral-mediated damage.[28] High levels of inflammatory markers including macrophages and IL-6, which are linked with PTB, have also been found with SARS-CoV-2 infection.[29] Of particular importance is IL-6, circulating levels of which have been linked with COVID-19 severity.[30] Evidence also suggests that during the third trimester, anti-SARS-CoV-2 specific antibodies are less likely to transfer across the placenta compared with antibodies against other pathogens.[31] The same phenomenon has not been observed when the infection occurred in the second trimester, providing critical insights on the likelihood of time-specific vulnerability and disease pathogenesis.[31] These studies highlight the significance of timing of COVID-19 during pregnancy, which is not clearly understood.

Hispanics have been reported to be at an increased risk of adverse perinatal outcomes.[32 33] Preliminary evidence also suggests that Hispanics may be at an increased risk of COVID-19, although most of these studies are small and were largely from the USA[23 34–36]; except one.[37] Thus, there is a need to study both the risk of adverse perinatal outcomes in a large Hispanic population, and whether the risks vary by timing of COVID-19 during pregnancy.

This study uses a large population from Mexico, closely related to the Hispanic population in the USA, to examine two research questions. (1) Is maternal COVID-19 during pregnancy associated with adverse perinatal outcomes including PTB, LBW, SGA, large-for-gestational age (LGA) and fetal death and (2) whether the associations between COVID-19 and adverse outcomes vary by trimester when the infection occurred. Tmanuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology guideline and includes a checklist.

MATERIAL AND METHODS

Study population

The study employed a retrospective birth cohort from Mexico between January 2020 and November 2021. The Mexican Institute of Social Security (IMSS—Instituto Mexicano del Seguro Social) created an IMSS COVID-19 dataset that was used for this analysis. IMSS, a comprehensive and vertically integrated insurance and healthcare system inspired by the Bismarck Model, provides services to approximately 70 million individuals in Mexico.[38] The system's primary focus is on serving formal private sector employees and their dependents, which constitutes a significant proportion of the Mexican population. Students 18 years or older and self-employed individuals are also eligible for the IMSS services. During the COVID-19 pandemic, IMSS extended its services to non-beneficiaries as part of its response to the public health crisis.

For the study period, the IMSS social security dataset containing COVID-19 information was cross-referenced with the IMSS routine hospitalisation dataset, using national identifications numbers, to identify individuals who underwent SARS-CoV-2 testing while pregnant and subsequently delivered. The datasets comprised maternal age, indigenous status, marital status, smoking status, socioeconomic status, mode of delivery, COVID-19 symptoms, vaccinations and pre-existing conditions (eg, obesity, diabetes, hypertension, cardiovascular diseases, asthma, pneumonia and immunosuppressive disorders). Neonatal information comprised sex, gestational age at birth, birth weight and intrapartum complications. Additionally, the hospitalisation dataset provided information on hospitalisation, intubation, intensive care unit (ICU) admission and death.

The IMSS COVID-19 and routine hospitalisation datasets contained 2 996 438 and 3 473 439 records, respectively. Of these, 825 822 were suspected of COVID-19 and had a hospitalisation record during the study period (online supplemental figure 1). Among those, 399 951 hospitalisations were for deliveries, of which 48 079 were suspected of COVID-19 and 33 719 were tested. Of those tested, 33 325 were singletons, 393 were multiple gestations and 1 was missing. The overall sample for this analysis comprised 17 340 singleton pregnancies with complete covariate information and COVID-19 tests conducted during pregnancy (the remainder were tested either before or after the pregnancy (online supplemental figure 1). 33 pregnancies (0.002%) were tested more than once. Only singleton births were included to eliminate confounding by multiple gestations. We filtered COVID-19 cases during pregnancy using the test date, date of delivery and gestational age at birth. A woman was considered to be positive if she tested positive on either an RT-PCR or a rapid antigen test.[39] Mild COVID-19 disease was defined as a positive test with one or more of the mild symptoms (headache, pain swallowing, myalgia, arthralgia, rhinitis, fever or chill, nasal congestion, difficulty speaking, abdominal pain, conjunctivitis, dyspnoea, diarrhoea, chest pain, fast breathing, coryza, loss of smell or taste[40]). Severe COVID-19 disease was defined as a positive test with the presence of one or more of the following conditions: hospitalisation, intubation, ICU admission or death. Asymptomatic COVID-19 disease was defined as a positive test without mild symptoms or severe disease.

Outcomes

WHO definitions were used for PTB (birth at gestational age less than 37 completed weeks[41] and LBW (weight at birth below 2500 g[42]). Birth weight-for-gestational age z-scores were calculated using the Intergrowth-21 standards.[43] SGA and LGA were defined as birth weight-for-gestational age below 10th and above 90th percentiles, respectively.[44]

We used International Classification of Diseases, Tenth Revision (ICD-10) codes to identify stillbirth (P95), fetal death (O36.4), missed abortion (O02.1) and spontaneous abortion (O03) because IMSS originally used ICD-10. The vast majority (98.1%) of these were coded as fetal death, and we analysed it as one composite outcome.

Statistical analysis

We used the targeted maximum likelihood estimators (TMLE)[45] to quantify the associations, which has been shown to perform better in estimating associations and CIs while achieving optimal bias-variance trade-off in the event of model misspecification.[46] TMLE obtains the initial estimate and performs the updating step through the clever covariate using the estimated probabilities.[47] TMLE uses a semiparametric substitution estimator that is efficient, doubly robust and has advantages over other well-known semiparametric approaches such as the augmented inverse propensity weighted estimator.[48] TMLE approach does not assign a parametric form to the distribution of the data, rather it remains an element of the semiparametric model. The model is represented as $\psi(p_0)=E_{W,0}\ [E_0(Y|X=1,\ W)/E_0(Y|X=0,\ W)]$, where $\psi(p_0)$ is the parameter of interest (eg, risk ratio, RR) and is a function of the unknown probability distribution. Y represents an adverse perinatal outcome, X represents maternal COVID-19 (diseased=1, disease free=0), W represents a set of covariates, E_0 is the expected probability and $E_{W,0}$ is the average of all the observed covariates. A TMLE model first generates an initial estimate of the parameter using super learner algorithms and identifies the best model that minimises the squared error loss function. The second step refines the initial model by optimising the bias-variance trade-off. This procedure has been demonstrated to be robust because it reduces bias and improves efficiency.[49] TMLE has been shown to generate unbiased estimate when either the outcome or the exposure is inconsistently estimated.[50] This is a significant advantage of the TMLE model, as it is expected to provide an unbiased estimate, in the presence of exposure misclassification. The estimate from the TMLE was interpreted as an RR of an outcome if all participants in the study population were exposed versus all were unexposed. The models were adjusted for available and necessary potential confounders, as described in the directed acyclic graph (online supplemental figure 2).

We implemented an ensemble machine learning method, the super learner, to avoid imposing assumptions on the data. The super learner considers multiple machine learning models by evaluating the specified loss function in cross validation, then it leverages the most predictive model(s) by creating the best-weighted combination.[51] We considered both parametric and non-parametric candidate models to cover a wide model space. The candidates were ridge regression, least absolute shrinkage and selection operator (LASSO) regression, multivariate adaptive regression splines, random forest, extreme gradient boosting, generalised additive model and Bayesian generalised linear model.[48] We fit the TMLE models in the: (1) overall sample, (2) those with mild symptoms only and (3) those with severe conditions only. We also fit the TMLE models by trimester when COVID-19 was diagnosed, using the overall sample.

In a sensitivity analysis, we adjusted the TMLE models using area-level characteristics at the level of AGEB, equivalent of a census tract in Mexico (https://www.inegi.org.mx/programas/ccpv/2020/#Microdatos). We used data pertaining to the census tract in which a primary care facility was located. There were many characteristics, including proportions of the AGEB population from different religions, ethnicities, literacy levels, employment, residential ownership, health service affiliation, etc (online supplemental table 1). We used principal component analysis and selected the top three components that together described 87% of the total variation in the area level variables (online supplemental table 2). Early in the pandemic, the testing regimen in Mexico for SARS-CoV-2 was not universal, rather based on symptoms or potential exposure.[52] Thus, some asymptomatic pregnancies would not have been tested. In a second sensitivity analysis, we examined if lack of information on non-tested pregnancies could induce bias. To examine the potential bias that would have been induced by the unavailability of test status of all pregnancies, we applied predictive value weighting (PVW) recommended by Lyles and Lin.[53] As the PVW method has not been rigorously examined in the TMLE environment, we fit multilevel logistic regression following the original method. We assumed several scenarios of non-tested pregnancies (between 0% and 30%) using non-differential and differential distributional assumptions by COVID-19 status. The upper level of 30% was based on a recent meta-analysis.[54] In the non-differential distribution, we assumed an equal proportion of non-tested pregnancies were missing in the negative and positive groups. In the differential assumption, we assumed unequal proportions are missing in the negative and positive groups. We re-estimated the expected true proportion of COVID-19 and the corresponding sensitivity and specificity for each scenario, ensuring that the observed proportion (π) is smaller than the sensitivity and greater than 1–specificity (a conditional requirement). Next, we replicated the data for several combinational levels of outcome, exposure and covariates with one set hypothetically assigned as exposed and another as unexposed. Finally, we fit the models with this new dataset to obtain new estimates that accounted for missing non-tested pregnancies. All hypothesis tests were two sided at the 5% significance level. The analysis was conducted in STATA V.17.0 and R.

Patient and public involvement

Procedures and methods followed the IMSS research guidelines. Anonymised data were used for analysis. Research questions and outcome measures were chosen in consultation, to answer questions of key concern to study partners to understand the potential effect of

Table 1 Characteristics of the birth cohort in Mexico, January 2020–November 2021

	With COVID-19 test, n (%)*	
	Negative	Positive
Total singleton pregnancies	12218	5122
Newborn characteristics		
Preterm birth	1381 (11.3)	574 (11.2)
Low birth weight	1288 (10.5)	566 (11.1)
Small-for-gestational age	1155 (9.5)	509 (9.9)
Large-for-gestational age	1451 (11.9)	624 (12.2)
Fetal death	71 (0.6)	34 (0.7)
Female	5981 (49.0)	2543 (49.6)
Maternal characteristics		
Maternal age (in years)		
12–17	157 (1.3)	52 (1.0)
18–29	8341 (68.3)	3212 (62.7)
30–34	2372 (19.4)	1142 (22.3)
35–39	1107 (9.1)	574 (11.2)
40–44	233 (1.9)	138 (2.7)
45 or over	8 (0.1)	4 (0.1)
Caesarean section	5373 (44.0)	2309 (45.1)
Ever smoker	226 (1.8)	93 (1.8)
Pre-existing health conditions		
Chronic obstructive pulmonary disease	6 (0.1)	4 (0.1)
Asthma	214 (1.8)	81 (1.6)
Diabetes	308 (2.5)	158 (3.1)
Obesity	711 (5.8)	342 (6.7)
Hypertension	296 (2.4)	124 (2.4)
Cardiovascular disease	25 (0.2)	5 (0.1)
Anaemia	6 (0.1)	2 (<0.1)
Liver diseases	2 (0.02)	0 (0)
Neurological disorder	5 (0.04)	2 (<0.1)
Immunosuppressive sisorder	35 (0.3)	15 (0.3)
Anyone of the above pre-existing conditions	1343 (11.0)	622 (12.1)
No pre-existing conditions	10875 (89.0)	4500 (87.9)

*Percentages are based on the column totals presented in the first row.

COVID-19 on pregnancy and the newborn. Patients were not involved in the design or conduct of the study, other than being a participant. Study results were shared with the in-country teams. However, results were not disseminated directly to women.

RESULTS

In the overall sample of 17340 singleton pregnancies, 30% or 5122 tested positive. Among those who tested positive, about 11% had PTB, 11% had LBW, 10% had SGA, 12% had LGA babies and 0.7% experienced fetal demise, which was comparable with the negative group (table 1). Those who tested positive were slightly older, compared with those who tested negative. Similarly, a slightly higher proportion of those who tested positive had any one or more pre-existing conditions (12%), compared with those who tested negative (11%) (table 1).

Of those who tested positive, 2% were asymptomatic, 87% had mild symptoms and 10% had severe COVID-19 disease (table 2). Among those who tested negative, 3% had no symptoms, 93% had mild symptoms and 4% had to be hospitalised (table 2).

In the overall sample as well as among those with mild symptoms, there was no positive association between COVID-19 and any of the adverse outcomes (table 3). A negative association was observed between those with

Table 2 Distribution of the mild and severe maternal COVID-19 in the birth cohort in Mexico, January 2020–November 2021

	COVID-19 status (N=17 340)	
	Negative, n (%)*	Positive, n (%)*
Total	12 218	5122
No symptoms	367 (3.0)	124 (2.4)
Mild symptoms†	11 321 (92.7)	4468 (87.2)
Severe conditions‡	530 (4.3)	530 (10.3)
Hospitalisation	530 (4.3)	529 (10.3)
Intensive care unit admission	2 (0.02)	10 (0.2)
Intubation	0 (0.0)	18 (0.4)
Death	1 (0.01)	14 (0.3)

*Proportions are based on the column total.
†Mild symptoms were defined as headache, pain swallowing, myalgia, arthralgia, rhinitis, fever or chill, nasal congestion, difficulty speaking, abdominal pain, conjunctivitis, dyspnoea, diarrhoea, chest pain, fast breathing, coryza, loss of smell or taste. Those who had one or more of these symptoms and tested positive for COVID-19 were identified as mild disease.
‡Severe condition was defined as hospitalisation, ICU admission, intubation or death. The numbers in the four categories will not add up to the total for severe disease because of overlap. Those who had one or more of these severe conditions and tested positive for COVID-19 were identified as severe disease.

only mild disease and PTB, RR=0.89 (95% CI 0.80 to 0.99, table 3). Among those with severe conditions, COVID-19 was positively associated with LGA, RR=1.53 (95% CI 1.07 to 2.19, table 3), and for the other outcomes the estimates indicate the possibility of positive associations, although the CIs included one (PTB 1.25, 95% CI 0.97 to 1.60; LBW 1.21, 95% CI 0.94 to 1.56 and SGA 1.15, 95% CI 0.82 to 1.60, table 3). Adjustment for the area-level characteristics, did not change the results for COVID-19 and perinatal outcomes in the overall sample, with mild symptoms or with severe conditions (online supplemental table 3).

In the trimester-specific analysis using the overall sample, COVID-19 in the first trimester was associated with fetal death, RR 2.36 (95% CI 1.04 to 5.36, table 4). For the other outcomes, there was no clear association for any specific trimester. However, the estimates suggest a possibility that COVID-19 in the third trimester may be associated with PTB (1.10, 95% CI 0.92 to 1.30), LBW (1.13, 95% CI 0.95 to 1.33) and SGA (1.11, 95% CI 0.95 to 1.30), although the CIs included one (table 4). Adjustment for the area-level characteristics, did not change the trimester-specific associations for COVID-19 and perinatal outcomes in the overall sample. However, the adjustment of made the association for fetal death stronger, RR=2.83 (95% CI 1.23 to 6.54) (online supplemental table 4).

Figure 1 demonstrates potential bias induced by missing non-tested pregnancies. In the first scenario, when there is no true association (ie, OR=1) and non-tested pregnancies are missing equally in both positive and negative groups, the magnitude of bias increases marginally with an increasing proportion of non-tested pregnancies (figure 1A). In other words, the bias is relatively small when the OR is close to 1, but as OR increases, the bias increases non-linearly with an increasing proportion of missingness (figure 1A). This analysis demonstrates that missing non-tested pregnancies is likely to induce bias away from the null, and the magnitude of the bias depends on the association as well as on the proportion of the non-tested pregnancies, for example, an OR of 1.09 increases to 1.38 when the proportion missing increases from 0% to 30%, respectively. In the second scenario, when all the non-tested pregnancies are missing from the positive and none are missing from the negative group,

Table 3 Adjusted association (risk ratios (RRs), 95% CI) between COVID-19 and adverse perinatal outcomes in a Mexican birth cohort of singleton pregnancies, January 2020–November 2021

	Overall sample *		Mild symptoms †		Severe conditions ‡	
	n_1 (%)	RR (95% CI)	n_2 (%)	RR (95% CI)	n_3 (%)	RR (95% CI)
Targeted maximum likelihood estimation§§	n=17 340		n=15 789		n=1060	
Preterm birth	1955 (11.27)	0.96 (0.88 to 1.06)	1636 (10.36)	0.89 (0.80 to 0.99)	116 (10.94)	1.25 (0.97 to 1.60)
Low birth weight	1854 (10.69)	1.02 (0.93 to 1.12)	1551 (8.95)	0.96 (0.87 to 1.07)	110 (10.38)	1.21 (0.94 to 1.56)
Small-for-gestational age	1664 (9.59)	1.05 (0.96 to 1.16)	1392 (8.03)	1.03 (0.93 to 1.15)	99 (9.31)	1.15 (0.82 to 1.60)
Large-for-gestational age	2075 (11.97)	1.01 (0.93 to 1.11)	1736 (10.01)	1.00 (0.91 to 1.10)	123 (11.62)	1.53 (1.07 to 2.19)
Fetal death	105 (0.01)	1.04 (0.68 to 1.58)	88 (0.56)	1.04 (0.66 to 1.63)	6 (0.59)	–¶

*All pregnant women who received a test for SARS-CoV-2 and were either positive or negative.
†Pregnancies with COVID-19 test and with mild symptoms.
‡Pregnancies with COVID-19 test and with severe conditions (hospitalisation, intensive care unit admission, intubation, death).
§Adjusted for sex of the newborn, maternal age, maternal smoking, mode of delivery and pre-existing conditions (chronic obstructive pulmonary disease, diabetes, asthma, obesity, hypertension, anaemia, immunosuppressive disorder, liver disease, neurological disorder).
¶The total number of fetal deaths was not enough to generate stable estimates with confidence limits.
ICU, intensive care unit.

Table 4 Trimester specific associations (risk ratios (RRs), 95% CI) between COVID-19 and adverse perinatal outcomes in a Mexican birth cohort,* January 2020–November 2021

	Trimester 1	Trimester 2	Trimester 3
Targeted maximum likelihood estimation ††	n=2767	n=6483	n=6095
Preterm birth	1.02 (0.81 to 1.28)	0.86 (0.73 to 1.01)	1.10 (0.92 to 1.30)
Low birth weight	1.02 (0.80 to 1.30)	0.98 (0.84 to 1.14)	1.13 (0.95 to 1.33)
Small-for-gestational age	0.84 (0.63 to 1.12)	1.05 (0.89 to 1.24)	1.11 (0.95 to 1.30)
Large-for-gestational age	1.09 (0.87 to 1.36)	1.03 (0.88 to 1.19)	0.99 (0.85 to 1.15)
Fetal death	2.36 (1.04 to 5.36)	0.99 (0.48 to 2.05)	0.80 (0.33 to 1.91)

*All singleton pregnancies with a COVID-19 test.
†Adjusted for sex of the newborn, maternal age, maternal smoking, mode of delivery and pre-existing conditions (chronic obstructive pulmonary disease, diabetes, asthma, obesity, hypertension, anaemia, immunosuppressive disorder, liver disease, neurological disorder).

the induced bias is relatively small, though it is still away from the null, regardless of the magnitude of the association (figure 1B). In the third scenario, when most of the non-tested pregnancies are missing from the negative group and none from the positive group, induced bias increases non-linearly with increasing OR, as the proportion of non-tested pregnancies increases (figure 1C). However, the magnitude of bias in the third scenario is slightly smaller than in the first (figure 1A,C).

DISCUSSION

This study investigated the association between COVID-19 disease during pregnancy and adverse perinatal outcomes among singleton deliveries in a large Mexican birth cohort. We found no evidence of association between COVID-19 and any of the outcomes in the overall sample. Restricting the sample to those with mild symptoms, we found no evidence of positive association, but we found a negative association between COVID-19 and PTB. Among those with severe conditions, a positive association was observed between COVID-19 and LGA. Although we did not find associations between severe COVID-19 and other investigated outcomes, the results indicate such possibility, because the point estimates were greater than 1 and the CIs are more compatible with a potential association in even larger cohorts.[55] COVID-19 in the first trimester was positively associated with fetal death. There was no association between COVID-19 in the third trimester and PTB, LBW and SGA, but the point estimates and the CIs suggest that there might be an association in a larger sample. To our knowledge, this is the first analysis to demonstrate the potential impact of missing non-tested pregnancies, which could bias estimates away from null. The magnitude of bias depends on the overall proportion missing, relative proportion missing in the positive and negative groups, and on the true underlying risk.

The positive association with LGA is not explained by pre-existing diabetes because adjusting the model for pre-existing diabetes does not change the result (1.54, 95% CI 1.03 to 2.31). However, undiagnosed cases of gestational diabetes could be an underlying reason for the association with LGA. Lockdowns and fear of contracting the infection during the pandemic likely modified health seeking behaviour, making it burdensome to get timely diagnosis and treatment for pregnancy complications including gestational diabetes. In April 2020, the Government of Mexico announced pregnant women to 'stay at home' (https://www.imss.gob.mx/prensa/archivo/202004/223) because of their increased vulnerability and to reduce the risk of infection. Lack of exercise and an increase in sedentary behaviour during the pandemic could have led to excess gestational weight gain without leading to clinical disease. Excess weight gain during pregnancy and increase in gestational diabetes, both risk factors for severe COVID-19 and LGA,[56] have been observed during the pandemic among Hispanics.[57 58] Further, COVID-19 early in pregnancy may have increased the risk of fetal death due to heightened antibody reaction leading to rejection of the fetus. Pandemic's effect in limiting or delaying prenatal care leading to a delay in identification of high-risk pregnancies could be an alternative explanation for fetal death. These associations and the vulnerability of the first trimester infection should be further investigated in different populations.

A comparison of our findings with other studies is tenuous because of differences in study size, setting and participant characteristics including race and ethnicity. Nonetheless, we present some studies for comparison. COVID-19 positivity among pregnant women in this study (30%) is comparable to that observed in Mexico City (29%–33%).[37] Proportions of LBW and PTB in Mexico were both at 7% in 2019, whereas in this study they were both at 10%.[59 60] Stillbirth rate was 7 per 1000 births, and the proportion of macrosomia (birth weight >4000 g) was 3%, compared with 6 per 1000 births and 3%, respectively, in this study.[59 61] The findings of no associations are consistent with several others.[14 17 19 24 25 62 63] An infection by itself may not be a risk factor unless it occurs very early in pregnancy. The association between severe COVID-19 and LGA (1.53) is similar to the results reported by Munda *et al* (1.24) and Simon *et al* (1.38), though their associations were smaller in magnitude and

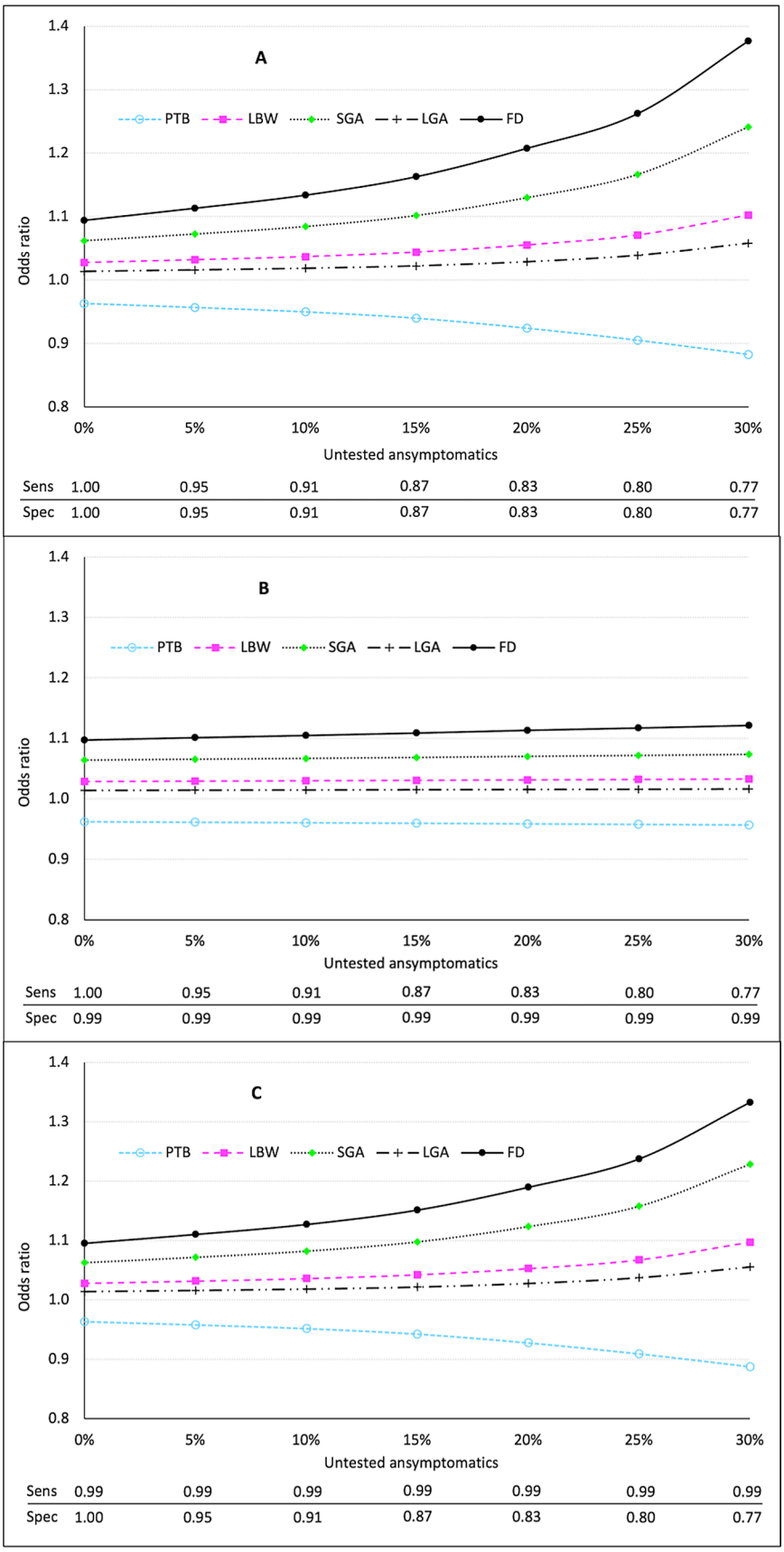

Figure 1 Potential bias that may have been induced by pregnancies that were not tested : (A) non-tested pregnancies are missing equally in both COVID-19 positive and negative groups; (B) non-tested pregnancies are missing more in the positive group; and (C) non-tested pregnancies are missing more in the negative group. PTB, preterm birth; LBW, low birth weight; SGA, small-for-gestational age; LGA, large-for-gestational age; FD, fetal death.

not statistically significant.[57 64] A higher proportion of macrosomia (12%) was reported among women who had pregnancies during lockdown, compared with pregnancies (9%) at the same time the preceding year.[65] However, another study did not find difference in the proportions of LGA between prepandemic and pandemic epochs, as well as between those who tested positive or negative for SARS-Cov-2.[62] The negative association observed for PTB, though consistent with a large meta-analysis comparing prepandemic with pandemic epochs, remains intriguing and we have no clear explanation.[66] Several studies have reported association between COVID-19 and fetal death.[67] A multicentre cohort study reported association between first trimester COVID-19 and stillbirth.[68] Consistent with our findings, the study concluded that mild COVID-19 is unlikely to affect perinatal outcomes and first trimester infection is an important risk factor.[68]

The results should be viewed in light of potential alternative explanations. Several SARS-CoV-2 variants, differing in infectivity and contagiousness, were prevalent during the study. Additionally, vaccines likely conferred some protection as they were rolled out. Thus, the duration for which pregnancies were at risk as well as the levels of risk, likely differed during the start and end of the study, which could induce bias. Although we cannot rule out the possibility of selection bias among those who were tested versus not tested, a comparison of the overall sample with those who had a COVID-19 test anytime, and those who delivered during the study period but were not tested, appears to be largely comparable (online supplemental table 5). Furthermore, we do not know how many pregnancies were not tested and whether those not tested were more in one group than the other. To protect the unborn, instinctively a pregnant woman would get herself tested after potential exposure or if symptoms were noticed. Thus, non-tested pregnancies could be more in the negative group, which could have affected the results.

Regardless, the study has several strengths, key among which is the large Mexican population, closely resembling the Hispanic population in the USA, and availability of individual as well as area-level characteristics. Dates of tests, date of delivery and gestational age, allowed us to examine associations by trimester. Validity of the outcome and covariate data is demonstrated by the associations observed with known risk factors (online supplemental table 6). Finally, we have also shown how missing non-tested pregnancies may have affected the results.

There are several limitations that should be considered with the resulting need for caution regarding the generalisability of the results. Our study population was limited to women who received care from the IMSS, were suspected of COVID-19, and were tested. Especially early in the pandemic, many people suspected of COVID-19 were not tested and the results we observe may be different in the non-tested population. Caution should be exercised in extrapolating the findings to the entire population of women giving birth in Mexico. Generally, women deliver at an IMSS facility because they or their partner are employed in the formal private sector. Thus, the Mexican women who deliver elsewhere are likely to be poorer (most) or richer (few) than the ones who deliver at an IMSS facility. We may have missed a small number of pregnant women due to the subrogation agreement whereby 28 000 IMSS patients over 37 weeks delivered in private facilities. The sample with severe COVID-19 was small, which likely affected precision of the results. We did not have genotype data, hence an analysis by SARS-CoV-2 variants could not be undertaken. Given the study period, this study most likely included the alpha (B.1.1.7), beta (B.1.351), gamma (P.1) and delta (B.1.617.2) variants. Due to data unavailability, we had to use a mixed group for fetal death. We acknowledge that spontaneous abortions are characteristically different from stillbirths, but we were unable to analyse them separately because of lack of granular data. Finally, we did not have gestational diabetes and gestational weight gain data, which are important risk factors. Thus, there could be some residual confounding.

CONCLUSIONS

The findings from this Mexican cohort study suggest that in the overall sample there was no evidence of an association between COVID-19 and adverse perinatal outcomes. However, mild COVID-19 was negatively associated with PTB. Severe COVID-19 was positively associated with LGA, and it may increase the risk of adverse perinatal outcomes. Furthermore, COVID-19 in the first trimester was positively associated with fetal death, suggesting that it could be a high-risk period. The study also demonstrates that missing non-tested pregnancies could bias the estimates, which depend on the proportion and the group (positive or negative) from which these are missing, as well as on the true risk.

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