Maternal and perinatal outcomes in high compared to low risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection (phase 2): the World Association of Perinatal Medicine working group on coronavirus disease 2019

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Cite this article as: D'Antonio F, Sen C, Mascio DD, et al. Maternal and perinatal outcomes in high compared to low risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection (phase 2): the World Association of Perinatal Medicine working group on coronavirus disease 2019. Am J Obstet Gynecol MFM 2021;3:100329.

2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2021.100329

BACKGROUND: It has still to be ascertained whether severe acute respiratory syndrome coronavirus 2 infection in pregnancy is associated with worse maternal and fetal outcomes compared to low risk gestations.

OBJECTIVE: This study aimed to evaluate maternal and perinatal outcomes in high- and low-risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection.

STUDY DESIGN: This was a multinational retrospective cohort study involving women with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection from 76 centers from 25 countries in Europe, the United States, South America, Asia, and Australia from April 4, 2020, to October 28, 2020. The primary outcome was a composite measure of maternal mortality and morbidity, including admission to the intensive care unit, use of mechanical ventilation, or death. The secondary outcome was a composite measure of adverse perinatal outcome, including miscarriage, fetal loss, neonatal and perinatal death, and admission to the neonatal intensive care unit. All outcomes were assessed in high- and low-risk pregnancies. Pregnancies were considered high risk in case of either preexisting chronic medical conditions in pregnancy or obstetrical disorders occurring in pregnancy. The Fisher exact test and logistic regression analysis were used to analyze the data.

RESULTS: A total of 887 singleton pregnancies who tested positive for severe acute respiratory syndrome coronavirus 2 infection using reverse transcription-polymerase chain reaction of nasal and pharyngeal swab specimens were included in the study. The risk of composite adverse maternal outcomes was higher in high-risk pregnancies than in low-risk pregnancies (odds ratio, 1.52; 95% confidence interval, 1.03−2.24; *P*=.035). In addition, women carrying high-risk pregnancies were at higher risk of hospital admission (odds ratio, 1.48; 95% confidence interval, 1.07−2.04; *P*=.002), presence of severe respiratory symptoms (odds ratio, 2.13; 95% confidence interval, 0.41−3.21; *P*=.001), admission to the intensive care unit (odds ratio, 2.63; 95% confidence interval, 1.42−4.88), and invasive mechanical ventilation (odds ratio, 2.65; 95% confidence interval, 1.19−5.94; *P*=.002). When exploring perinatal outcomes, high-risk pregnancies were at high risk of adverse perinatal outcomes (odds ratio, 1.78; 95% confidence interval, 0.15−2.72; *P*=.009). However, such association was mainly because of the higher incidence of miscarriage in high-risk pregnancies compared with that in low-risk pregnancies (5.3% vs 1.6%, *P*=.008); furthermore, there was no difference in other explored outcomes between the 2 study groups. At logistic regression analysis, maternal age (odds ratio, 1.12; 95% confidence interval, 1.02−1.22; *P*=.023) and high-risk pregnancy (odds ratio, 4.21; 95% confidence interval, 3.90−5.11; *P*<.001) were independently associated with adverse maternal outcomes.

CONCLUSION: High-risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection were at higher risk of adverse maternal outcomes than low-risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection.

Key words: coronavirus, coronavirus disease 2019, infection, pregnancy, severe acute respiratory syndrome coronavirus 2

AJOG MFM at a Glance

Why was this study conducted?

To elucidate whether high-risk pregnancies complicated by SARS-CoV-2 infection are at higher risk of adverse outcome compared to low-risk gestations.

Key findings

High-risk pregnancies complicated by SARS-CoV-2 infection are at higher risk of severe respiratory symptoms, invasive mechanical ventilation and admission to intensive care unit compared to low-risk gestations.

What does this add to what is known?

High-risk pregnancy represents an independent risk factor for severe SARS-CoV-2 infection. Accurate risk stratification in these women is warranted in order to maximize maternal outcome.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection spread toward the end of 2019 and nowadays is still a major issue of public health, with new cases of infection, hospitalization, admission to the intensive care unit (ICU), and death increasing daily worldwide.[1,2]

From the beginning of the pandemic, pregnant women have been claimed as having a higher risk of maternal mortality and morbidity compared with the general population.[3−9]

The severity of SARS-COV-2 infection in the general population has been reported to be significantly influenced by different risk factors. Among these, age and comorbidities were found to be the strongest predictors of hospital admission, critical illness, and mortality.[10]

Despite the multitude of reports published on SARS-CoV-2 infection during pregnancy, only few studies were designed to ascertain whether the presence of either preexisting or pregnancy-related conditions (ie, those usually considered high-risk pregnancies) might increase the risk of both maternal and fetal adverse outcomes.

Thus, the aim of this secondary analysis was to elucidate whether high-risk pregnancies were at higher risk of adverse maternal and perinatal outcomes in a multinational cohort of pregnant women who tested positive for SARS-CoV-2 infection.

Methods

Study design and participants

This was a multinational, prospective cohort study involving all pregnant women with a laboratory-confirmed SARS-CoV-2 infection, diagnosed from April 4, 2020, to October 28, 2020. This study was designed as an open and web-based database study in 76 centers from 25 countries (Argentina, Australia, Belgium, Brazil, Colombia, the Czech

Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, the Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and the United States) by the World Association of Perinatal Medicine (WAPM) working group on coronavirus disease 2019 (COVID-19). The study was endorsed by the WAPM. The first phase of the study has already been published, which composed of data from April 4, 2020, to June 1, 2020.[4] After that, some additional information for the study was added to the database and reevaluated by the contributors accordingly for the new database as WAPM COVID-19 Study Phase 2. Only confirmed cases with a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test were included in the evaluation.

SARS-CoV-2 was diagnosed on the basis of the World Health Organization interim guidance.[11] A confirmed case of SARS-CoV-2 infection was defined as a positive result on a RT-PCR assay of nasal and pharyngeal swab specimens.[12,13] The inclusion criteria were women who tested positive for SARS-CoV-2 after an RT-PCR assay of nasal and pharyngeal swab specimens because of symptoms or exposure to infected individuals. Neonates from mothers who are positive of SARS-CoV-2 were usually tested within 24 hours after delivery with an RT-PCR assay of nasal and pharyngeal swab specimens.

Data on current exposure history, clinical symptoms or signs, laboratory findings, and maternal and perinatal outcomes were collected. All medical records were anonymized and sent to the coordinator center at the University of Naples Federico II (Naples, Italy) through the WAPM data platform or via an encrypted research electronic data capture data management platform. Data were entered into a computerized database and cross-checked. In case of missing data, requests for clarification were sent to the coordinator of each participating center.

Outcomes

The primary outcome of this study was to compare the incidence of a composite measure of maternal mortality and morbidity, including at least 1 of the following: admission to the ICU, use of mechanical ventilation (defined as intubation, need for continuous positive airway pressure, extracorporeal membrane oxygenation), severe respiratory symptoms (including dyspnea and shortness of breath), or death in high-risk vs low-risk pregnancies.

The secondary outcomes were a composite score of adverse perinatal outcome, including miscarriage, intrauterine death, neonatal death (NND), admission to the neonatal ICU (NICU), and individual components of both primary and secondary outcomes. Miscarriage was defined as pregnancy loss before 22 weeks of gestation or fetal loss at or after 22 weeks of gestation, whereas NND was defined as death of a live-born infant within the first 28 days of life. Perinatal death was defined as fetal loss and NND.

Further details on the criteria for maternal admission to the ICU and neonatal admission to the NICU are more extensively described elsewhere.[9]

All these outcomes were assessed in high-risk pregnancies and compared with outcomes in low-risk pregnancies. Pregnancies were considered high risk in case of either preexisting chronic medical conditions in pregnancy (pregestational diabetes mellitus, chronic hypertension, or autoimmune disease) or obstetrical disorders occurring in pregnancy (preeclampsia, gestational hypertension, or gestational diabetes mellitus). Regarding the specific medical complications affecting pregnancy, chronic hypertension was defined as hypertension that precedes pregnancy or was present on at least 2 occasions before the 20th week of gestation. Preeclampsia was defined as the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or after birth in a previously normotensive woman, whereas gestational hypertension was defined as a blood pressure of ≥140/90 mm Hg on 2 occasions (at least 4 hours apart) during pregnancy after 20 weeks of gestation in a previously normotensive patient, without the presence of proteinuria or other clinical features suggestive of preeclampsia. Finally, gestational diabetes mellitus was defined as any degree of glucose intolerance with onset or first recognition during pregnancy after 75 g or 100 g of oral glucose tolerance test according to each country-specific guideline.

To elucidate the rate of vertical transmission, all newborns included in this cohort were tested at birth.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 19.0; IBM Inc, Armonk, NY) and using Stata (version 13.1; Stata Corp, College Station, TX). Continuous variables were reported as mean±standard deviation, whereas categorical variables were reported as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-squared test with continuity correction. Comparisons between the groups were performed with the use of the *t* test to test group means by assuming equal within-group variances for parametric data and with the use of Wilcoxon and Mann-Whitney tests for nonparametric data. Multivariate analysis was performed to evaluate potential predictors of the primary outcome. Logistic regression was reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). A *P* value of <.05 was considered statistically significant.

Results

General characteristics of the included women

During the study period, 887 women with singleton viable high-risk pregnancies (122 with chronic preexisting complications and 86 with medical complications occurring during gestation) at the time of assessment, positive for SARS-CoV-2 after RT-PCR of nasal and pharyngeal swab specimens, in 72 centers from 22 countries were included in the study.

TABLE 1
Comparison of different characteristics in high- vs low-risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection

Characteristic	High-risk pregnancies(n=208)	No high-risk pregnancies(n=679)	*P* value
Maternal and pregnancy characteristics			
Maternal age	34.16±6.80	31.39±5.50	<.001[a]
Gestational age at diagnosis of infection (wk)	30.26±9.80	29.65±9.60	.425
Nulliparity	75 (36.1)	219 (32.3)	.313
Smoking before or during pregnancy	11 (5.3)	21 (3.1)	.140
Preterm birth at <37 wk of gestation	33 (15.9)	61 (9.0)	.007[a]
Preterm birth at <34 wk of gestation	14 (6.7)	27 (4.0)	.129
Vaginal delivery	145 (69.7)	527 (77.6)	.026[a]
Cesarean delivery	63 (30.3)	152 (22.4)	.026[a]
Clinical, radiological and laboratory findings			
Symptomatic infection	106 (51.0)	411 (60.5)	.016[a]
Asymptomatic infection	102 (49.0)	268 (39.5)	.016[a]
Fever	50 (24.0)	206 (30.3)	.081
High-grade fever	20 (9.6)	14 (2.1)	<.001[a]
Cough	52 (25.0)	185 (27.2)	.591
Myalgia	28 (13.5)	129 (19.0)	.078
Anosmia	11 (5.3)	47 (6.9)	.521
GI symptoms	4 (1.9)	23 (3.9)	.360
Positive chest CT scan	34 (16.3)	20 (2.9)	<.001[a]
Lymphopenia	109 (52.4)	311 (45.8)	.096
Thrombocytopenia	27 (13.0)	31 (4.6)	<.001[a]
Increased LDH levels	29 (13.9)	24 (3.5)	<.001[a]
Pharmacologic treatments			
LMWH	58 (27.9)	125 (18.4)	.139
Antibiotics	61 (29.3)	209 (30.8)	.731
Any antiviral drug	67 (32.2)	142 (20.9)	<.001[a]
Hydroxychloroquine	46 (22.1)	122 (18.0)	.189

Data are presented as number (percentage) or mean±standard deviation.

CT, computerized tomography; *LDH*, lactate dehydrogenase; *LMWH*, low-molecular-weight heparin.

[a] Values are statistically significant.

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General characteristics of the study population are reported in Table 1. Maternal age was higher in high-risk pregnancies than in low-risk pregnancies (34.16±6.80 vs 31.39±5.50; *P*<.001); however, there was no difference in the mean gestational age at diagnosis of infection (*P*=.425), nulliparity (*P*=.313), and smoking status (*P*=.140) (Table 1). Regarding the obstetrical outcomes, women with high-risk pregnancies had a higher incidence of preterm delivery at <37 weeks of gestation than women with non–high-risk pregnancies (15.9% vs 9.0%; *P*=.007); however, there was no difference between the 2 groups regarding the occurrence of preterm delivery at <34 weeks of gestation. Furthermore, high-risk pregnancies were more likely delivered by cesarean delivery compared with controls (30.3% vs 22.4%; *P*=.026). In addition, there were 3 cases of maternal deaths. The first maternal death occurred in a high-risk pregnancy with type II diabetes mellitus. The woman presented to the hospital at 33 weeks of gestation with stillbirth. The woman was febrile and unconscious. Chest radiography showed pulmonary infiltrates and atelectasis with elevated left

TABLE 2
Comparison of the different maternal and fetal outcomes in high- vs low-risk pregnancies complicated by severe acute respiratory syndrome coronavirus 2 infection

Outcome	High-risk pregnancies(n=208)	No high-risk pregnancies(n=679)	*P* value
Composite adverse maternal outcome	46 (22.1)	107 (15.8)	.036[a]
In-hospital admission	85 (40.9)	216 (31.8)	.019[a]
Severe respiratory symptoms	44 (21.2)	76 (11.2)	<.001[a]
Admission to the intensive care unit	19 (9.1)	25 (3.7)	.003[a]
Invasive ventilation	11 (5.3)	14 (2.1)	.027[a]
Composite adverse fetal outcome	37 (17.8)	74 (10.9)	.012[a]
Miscarriage	11 (5.3)	11 (1.6)	.008[a]
Intrauterine death	2 (1.0)	3 (0.4)	.334
Neonatal death	2 (1.0)	6 (0.8)	1.000
Perinatal death	4 (2.0)	9 (1.2)	.516
Admission to the neonatal intensive care unit	18 (8.7)	54 (8.0)	.772

[a] Values are statistically significant.

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hemidiaphragm. The woman was admitted to the ICU and intubated but died with acute kidney injury and cardiac arrest. The second and third deaths occurred in 2 non–high-risk pregnant women aged 25 and 27 years old, respectively, presenting to the emergency department with severe respiratory symptoms requiring admission to the ICU. Details of these 3 maternal deaths are reported in a previous study from our group.[4]

The risk of composite adverse maternal outcomes was higher in high-risk pregnancies than in low-risk pregnancies with an OR of 1.52 (95% CI, 1.03–2.24; *P*=.035) (Table 2). In addition, women carrying high-risk pregnancies were at higher risk of the following: admission to the hospital (OR, 1.48; 95% CI, 1.07–2.04; *P*=.002), presence of severe respiratory symptoms (aOR, 2.13; 95% CI, 1.41–3.21; *P*=.001), admission to the ICU (aOR, 2.63; 95% CI, 1.42–4.88), and invasive mechanical ventilation (OR, 2.65; 95% CI, 1.19–5.94; *P*=.002).

When exploring perinatal outcomes, high-risk pregnancies were at high risk of adverse perinatal outcomes with an aOR of 1.78 (95% CI, 0.15–2.72; *P*=.009). However, such association was mainly because of the higher incidence of miscarriage in high-risk pregnancies than in low-risk pregnancies (5.3% vs 1.6%; *P*=.008); however, there was no difference in the occurrence of fetal loss (*P*=.334), NND (*P*=1.000), perinatal death (*P*=.516), and admission to the NICU (*P*=.772) between high- and low-risk pregnancies complicated by SARS-CoV-2 infection.

At logistic regression analysis, maternal age (aOR, 1.12; 95% CI, 1.02–1.22 per 10 year increase; *P*=.023) and the presence of high-risk pregnancies (aOR, 4.21; 95% CI, 3.90–5.11; *P*<.001) were independently associated with adverse maternal outcomes; furthermore, maternal age (aOR, 1.33; 95% CI, 1.19–1.47 per 10 year increase; *P*=.019) was the only factor associated with adverse perinatal outcome.

Discussion

Main findings

This secondary analysis of the WAPM study—a multinational cohort study, including 388 pregnant women with confirmed SARS-CoV-2 infection from 72 centers—showed that the rates of composite adverse maternal outcomes, severe respiratory symptoms, and invasive ventilation in high-risk pregnancies were significantly higher than in low-risk pregnancies. Conversely, there was no difference found when assessing for fetal outcomes in high-risk pregnancies compared with that in low-risk pregnancies.

Strengths and limitations

The strength and limitation of this analysis were essentially those inherent in the primary analysis.[4] The enrollment of only women with laboratory-confirmed SARS-CoV-2 infection, the large sample, the inclusion of both university and community hospitals from different countries, and the multitude of outcomes explored represented the major strengths of this study. The major limitation of this study was that the study population mostly came from women referred for suspected SARS-CoV-2 infection, because of symptoms or exposure, and consequently tested for RT-PCR of nasal and pharyngeal swab specimens, thus leading to an intuitively lower percentage of asymptomatic women in the study cohort. More importantly, the inclusion of women mainly presenting with symptoms or being tested positive for close contact with people with SARS-CoV-2 represented an inclusion bias, and it may be entirely possible that the rate of adverse outcomes reported in women with high-risk pregnancy from this series may represent an overestimation of the

actual occurrence of these outcomes in the overall general population of pregnant women with SARS-CoV-2 infection. Another major limitation was represented by the fact that we could not stratify the analysis according to the specific pregnancy or prepregnancy comorbidity because the small number of cases per subgroup category would have affected the robustness of the results. Furthermore, different income levels of countries and healthcare systems and the heterogeneity in the management of both the mother and fetus might have independently affected perinatal outcomes. Finally, the contribution of each center in providing the data and definitions of the different pregnancy complications (ie, gestational diabetes mellitus) were not homogenous. In this scenario, it may be entirely possible that the study population included the most severe spectrum of SARS-CoV-2 infection in pregnancy.

Implications for clinical practice and research

Since the beginning of the pandemic outbreak, pregnancy has been extensively evaluated as a potential high-risk condition because of physiological changes that might predispose pregnant women to a more severe clinical course of COVID-19 compared with the nonpregnant population.[4,5]

One of the largest systematic reviews currently published on this topic showed that pregnant and recently pregnant women affected by COVID-19 were significantly more likely to need admission to the ICU and invasive ventilation than nonpregnant women of reproductive age and that increased maternal age, higher body mass index, chronic hypertension, and preexisting diabetes mellitus were all significantly associated with a more severe course of COVID-19 in pregnancy. Moreover, preexisting maternal comorbidities represented a risk factor for admission to the ICU and for invasive ventilation.[9]

The presence of higher risk of adverse outcomes in patients affected by COVID-19 is a well-known issue in the general population and has been reported early in the beginning of the pandemic: cardiovascular diseases, diabetes mellitus, hypertension, and obesity have been all shown to be strong predictors of mortality and severe morbidity in people with SARS-CoV-2 infection, particularly in patient with increasing age,[14–17] although the strength of this association persists when considering only young adults.[18,19]

The findings from this study confirmed what was previously shown in both the general population and pregnant women, as the presence of either preexisting or obstetrical conditions was associated with a significantly higher risk of composite adverse maternal outcomes, severe respiratory morbidity, and need for invasive ventilation. Conversely, the association between SARS-CoV-2 infection and high-risk pregnancy did not significantly influence perinatal outcomes.

Conclusions

In this study, high-risk pregnancies, complicated by SARS-CoV-2 infection, were at higher risk of adverse outcomes, mostly respiratory, than low-risk pregnancies. Accurate risk stratification of women presenting with suspected SARS-CoV-2 infection in pregnancy is warranted to identify a subset of women who may benefit from a tailored management, to improve maternal outcomes. ■

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Received Nov. 12, 2020; revised Feb. 1, 2021; accepted Feb. 10, 2021.

The authors report no conflict of interest.

Ethical Committee of Federico II University of Naples, number 145/2020.

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