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Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19

<https://doi.org/10.1515/jpm-2020-0355>

Received July 27, 2020; accepted August 21, 2020; published online September 25, 2020

Abstract

Objectives: To evaluate the strength of association between maternal and pregnancy characteristics and the risk of adverse perinatal outcomes in pregnancies with laboratory confirmed COVID-19.

Methods: Secondary analysis of a multinational, cohort study on all consecutive pregnant women with laboratory-confirmed COVID-19 from February 1, 2020 to April 30, 2020 from 73 centers from 22 different countries. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. The primary outcome was a composite adverse fetal outcome, defined as the presence of either abortion (pregnancy loss before 22 weeks of gestations), stillbirth (intrauterine fetal death after 22 weeks of

gestation), neonatal death (death of a live-born infant within the first 28 days of life), and perinatal death (either stillbirth or neonatal death). Logistic regression analysis was performed to evaluate parameters independently associated with the primary outcome. Logistic regression was reported as odds ratio (OR) with 95% confidence interval (CI).

Results: Mean gestational age at diagnosis was 30.6±9.5 weeks, with 8.0% of women being diagnosed in the first, 22.2% in the second and 69.8% in the third trimester of pregnancy. There were six miscarriage (2.3%), six intrauterine device (IUD) (2.3) and 5 (2.0%) neonatal deaths, with an overall rate of perinatal death of 4.2% (11/265), thus resulting into 17 cases experiencing and 226 not experiencing composite adverse fetal outcome. Neither stillbirths nor neonatal deaths had congenital anomalies found at antenatal or postnatal evaluation. Furthermore, none of the cases experiencing IUD had signs of impending demise at arterial or venous Doppler. Neonatal deaths were all considered as prematurity-related adverse events. Of the 250 live-born neonates, one (0.4%) was found positive at RT-PCR pharyngeal swabs performed after delivery. The mother was tested positive during the third trimester of pregnancy. The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. At logistic regression analysis, gestational age at diagnosis (OR: 0.85, 95% CI 0.8–0.9 per week increase; $p < 0.001$), birthweight (OR: 1.17, 95% CI 1.09–1.12.7 per 100 g decrease; $p = 0.012$) and maternal ventilatory support, including either need for oxygen or CPAP (OR: 4.12, 95% CI 2.3–7.9; $p = 0.001$) were independently associated with composite adverse fetal outcome.

Conclusions: Early gestational age at infection, maternal ventilatory supports and low birthweight are the main determinants of adverse perinatal outcomes in fetuses with maternal COVID-19 infection. Conversely, the risk of vertical transmission seems negligible.

Keywords: Coronavirus; perinatal mortality; perinatal morbidity.

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Introduction

Towards the end of 2019, a novel Coronavirus mutation - labelled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) - was identified as the cause of a respiratory illness called COVID-19, that suddenly became epidemic in China, and then dramatically spread in many other countries worldwide as a global pandemic [1–9].

Despite rigorous mitigation measures adopted by governments to reduce both the virus spread and its detrimental effects on healthcare systems and therefore on the whole worldwide economy [10], COVID-19 has currently affected about five millions of people with more than 300,000 deaths [11].

Although evidence is accumulating rapidly, there are still several outstanding issues that need to be settled soon regarding the effect of COVID-19 on perinatal outcomes to guide the antenatal counselling and management of women with COVID-19 during pregnancy.

In a large multinational cohort study, we have recently shown that COVID-19 in pregnant women is associated with low rate of maternal mortality, but 11.1% rate of admission to intensive care unit (ICU) [12].

However, an accurate risk stratification of women with COVID-19 is needed to ascertain the association between different maternal characteristics or clinical findings and adverse perinatal outcomes, in order to more appropriately tailor their management.

The primary aim of this study was to report perinatal outcome in pregnancies complicated by COVID-19 infection; the secondary aim was to elucidate the strength of association between maternal and pregnancy characteristics and the risk of adverse perinatal outcome in these pregnancies.

Materials and methods

Study design and participants

This is a secondary analysis of the World Association of Perinatal Medicine (WAPM) study [12]. The WAPM study was a multinational, cohort study on all consecutive pregnant women with laboratory-confirmed COVID-19 from February 1, 2020 to April 30, 2020 from 73 centers from 22 different countries (Argentina, Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, and United States)

COVID-19 was diagnosed on the basis of The World Health Organization (WHO) interim guidance [13]. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [14, 15].

The study was approved by the IRB of the University of Naples Federico II (April 2020, approval number: 145/2020).

A composite adverse fetal outcome was defined as the presence of either:

- Abortion, defined as pregnancy loss before 22 weeks of gestations,
- Stillbirth, defined as intrauterine fetal death after 22 weeks of gestation,
- Neonatal death, defined as death of a live-born infant within the first 28 days of life,
- Perinatal death, defined as either stillbirth or neonatal death.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Continuous variables were reported as means \pm standard deviation (SD), while categorical as numbers (percentage). Univariate comparisons of dichotomous data were performed with the use of the χ^2 -test with continuity correction. Comparisons between 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. We also planned to test the strength of association between different maternal and pregnancy characteristics, and clinical, radiological, and laboratory findings, with a composite adverse fetal outcome. Logistic regression analysis was also performed to evaluate parameters independently associated with a composite adverse fetal outcome. Logistic regression was reported as odds ratio (OR) with 95% confidence interval (CI). For the purpose of the analysis, this analysis was performed including only women with completed pregnancy. A p-value <0.05 was considered statistically significant.

Results

The WAPM study involved 388 singleton pregnancies positive to COVID-19 at RT-PCR nasal and pharyngeal swab, in 73 centers from 22 different countries.

Mean gestational age at diagnosis was 30.6 ± 9.5 weeks, with 8.0% of women being diagnosed in the first, 22.2% in the second and 69.8% in the third trimester of pregnancy. Included women were asymptomatic in 24.2% of cases. The most common symptom at the time of triage was cough (52.1%), followed by fever (44.1%), while shortness of breath was complained by 60 women (15.5%). 11.1% of women were admitted to ICU, and 6.4% requiring intubation. There were three cases of maternal deaths, accounting for a maternal mortality rate of 0.8% [12].

Evaluation of the potential risk factors associated with the occurrence of the composite adverse fetal outcome was performed only in women with completed pregnancy.

Table 1 shows perinatal outcomes from the WAPM study. There were six miscarriage (2.3%), six intrauterine

device (IUD) (2.3) and 5 (2.0%) neonatal deaths, with an overall rate of perinatal death of 4.2% (11/265), thus resulting into 17 cases experiencing and 248 not experiencing composite adverse fetal outcome. Neither stillbirths nor neonatal deaths had congenital anomalies found at antenatal or postnatal evaluation. Furthermore, none of the cases experiencing IUD had signs of impending demise at arterial or venous Doppler (reverse end diastolic flow in the umbilical artery, increased ductus venosus pulsatility index, absent or reverse a wave in the ductus venosus). Neonatal deaths were all considered as prematurity-related adverse events. Of the 250 live-born neonates, one (0.4%) was found positive at RT-PCR pharyngeal swabs performed after delivery. The mother was tested positive during the third trimester of pregnancy. The newborn was asymptomatic and had negative RT-PCR test after 14 days of life. Unfortunately, amniotic fluid was not tested, and specimens from placenta were not obtained, thus questioning whether the infection occurred *in utero* (antenatal vertical transmission) or after immediately prior or after birth (perinatal vertical transmission).

When exploring maternal and pregnancy characteristics, gestational age at diagnosis was lower (23.2 ± 10.9 vs. 35.0 ± 4.6 , $p < 0.001$) in fetuses with composite adverse outcome, while there was no difference in

maternal age at the infection between the two study groups. Similarly, the incidence of composite adverse fetal outcome was significantly higher when the infection occurred in the first trimester (35.3 vs. 2%, $p < 0.001$). The incidence of composite adverse fetal outcome was significantly higher in fetuses with lower birthweight (2007 ± 1014 g vs. 2939 ± 755 , $p < 0.001$), while it was similar in nulliparous women, women smoking during pregnancy or with chronic, pre-existing conditions, women undergone flu vaccination, and those with a positive CT scan.

When focusing on clinical, radiological and laboratory findings, maternal need for oxygen (41.2 vs. 17.3%, $p = 0.02$) and CPAP (29.4 vs. 8.5%, $p = 0.02$) were significantly associated with composite adverse fetal outcome

Finally, no difference was found when evaluating the effect different pharmacologic treatments (LMWH, azithromycin, antiviral drugs or hydroxychloroquine) on composite adverse fetal outcome

At logistic regression analysis, gestational age at diagnosis (OR: 0.85, 95% CI 0.8–0.9 per week increase; $p < 0.001$), birthweight (OR: 1.17, 95% CI 1.09–1.12.7 per 100 g decrease; $p = 0.012$) and maternal ventilatory support, including either need for oxygen or CPAP (OR: 4.12, 95% CI 2.3–7.9; $p = 0.001$) were independently associated with composite adverse fetal outcome.

Table 1: Perinatal outcomes from the WAPM study [12].

| Women with completed pregnancies (n=266) | | % (95% CI) |
|---|------|------------------|
| Elective termination of pregnancy | 3 | 1.1 (0.4–3.3) |
| Stillbirth | 6 | 2.3 (1.0–4.8) |
| Perinatal death | 11 | 4.1 (2.3–7.3) |
| IUGR | 10 | 3.8 (2.1–6.8) |
| Preterm birth | 70 | 26.3 (21.4–31.9) |
| Live-born infants | 251 | 94.4 (90.9–96.6) |
| Women with live-born infants (n=251) | | % (95% CI) |
| Possible vertical transmission | 1 | 0.4 (0.07–2.2) |
| Neonatal death ^a | 5 | 2.0 (0.9–4.6) |
| Admission to NICU | 69 | 27.5 (22.3–33.3) |
| Breastfeeding | 101 | 40.2 (34.4–46.4) |
| Skin to skin | 69 | 27.5 (22.3–33.3) |
| Low birth weight | 52 | 20.7 (16.2–26.2) |
| Cesarean delivery | 136 | 54.2 (48.0–60.2) |
| Spontaneous first-trimester abortion ^b | 6/31 | 19.4 (9.2–36.3) |
| Gestational age at delivery, years, mean \pm SD | | 37.2 \pm 3.9 |
| Birth weight, grams, mean \pm SD | | 2919 \pm 772 |

Data are presented as number (percentage) or as mean \pm standard deviation (SD). NICU, neonatal intensive care unit; LBW, low birth weight; IUGR, intrauterine growth restriction. ^aIncluding only live-born infants. ^bIncluding only women with first trimester infection.

Discussion

Summary of the main findings

The findings from this study showed that, in pregnancies complicated by COVID-19 infection, the rate of perinatal death was about 4%, mainly related to prematurity. Early gestational age at diagnosis, gestational age at diagnosis, birthweight and maternal ventilatory support were the only factors independently associated with adverse fetal outcome. Finally, the risk of vertical transmission was negligible.

Strengths and limitations

To our knowledge, this may be the largest cohort of COVID-19 during pregnancy published so far. Strengths and limitations of this secondary analysis are those inherent in the WAPM study. The enrollment of only of women with laboratory-confirmed COVID-19 and the inclusion of both University Hospitals and Community Hospitals from

different countries represent the major strengths of this study. The major limitation of the study is the incidence of the composite adverse perinatal outcome in the overall population is low, thus making our sample size potentially underpowered to draw any convincing evidence. Another limitation is the inclusion of only high-income and middle-income countries, and therefore we acknowledge that in low-income countries perinatal outcomes might be even worse [3].

Implications for clinical practice and research

COVID-19 has brought the scientific community into unprecedented times and currently represents the major global public health issue. Despite the growing number of reports published so far [16–18], evidence is still limited particularly when focusing on vulnerable conditions, such as pregnancy.

We have recently shown that COVID-19 in pregnant women is associated with low rate of maternal mortality, but 11.1% rate of admission to ICU. Furthermore, earlier gestational age at presentation, shortness of breath as presenting symptom, and increased lactate dehydrogenase (LDH) levels were independently associated with composite adverse maternal outcome including either admission to intensive care unit, use of mechanical ventilation or death [12].

In this secondary analysis, we planned to ascertain whether different maternal and pregnancy characteristics; clinical, laboratory or radiological findings and pharmacological treatments could be associated with serious adverse perinatal outcomes, including stillbirths and neonatal deaths, and we found that earlier gestational age at diagnosis, birthweight and maternal ventilatory support were independently associated with a composite adverse perinatal outcome.

Gestational age at diagnosis is a peculiar issue when assessing pregnancies affected by viral infections and the occurrence of the infection earlier in pregnancy is usually associated with worse fetal outcomes. In a large meta-analysis of cohort and case-control studies, maternal seasonal influenza or influenza-like illness in the first trimester was associated with a significantly higher risk of congenital abnormalities, such as cleft lip, neural tube defects, hydrocephaly, and congenital heart defects [19]. Moreover, recent data on women with a primary Cytomegalovirus infection and an infected child aged at least 1 year at the time of the analysis show that the infection can be severe only when the virus hits the fetus in the embryonic or early fetal period [20]. Alongside the high burden of fetal morbidity,

parvovirus B19 infection in the first trimester of pregnancy was associated with an increased risk of fetal loss [21] and fetal death is generally observed when the infection occurs before the completed 20 weeks of gestation [22].

These data are concordant with our results, as COVID-19 infection in the first trimester was significantly associated with the occurrence of a composite adverse fetal outcome, while there was no difference when the infection occurred during the second and the third trimester of pregnancy.

Therefore, longitudinal evaluation of pregnancies affected with COVID-19 is recommended to rule out any potential factor that may significantly impact short and long-term prognosis. In this scenario, the use of neurosonography and fetal magnetic resonance imaging (MRI), that has significantly spread in the past few years in several fields of maternal fetal medicine [23, 24], might be judiciously considered as useful imaging techniques for a complete fetal assessment.

Perinatal death is certainly one of the main concern of maternal fetal specialists. So far, the rate of both stillbirths and neonatal deaths has been reported to be slightly increased, although the majority of neonatal deaths are considered to be related to prematurity or to critically ill mothers [3, 25, 26].

COVID-19 may predispose the general population to a thrombotic condition, both in the venous and arterial circulations, due to inflammation, platelet activation, endothelial dysfunction, and stasis [27, 28]. This COVID-19 related hypercoagulability state might intuitively assume an important role in pregnancy due to its inherent prothrombotic state, and might represent a possible cause of the small increase of the rate of stillbirths compared with the baseline population [29–32].

However, we acknowledge that the sample size potentially underpowered for this outcome and the lack of effect of low molecular weight heparin cast some doubt on this hypothesis and do not allow to obtain robust evidence on the risk of stillbirth in pregnancies affected by COVID-19.

Conclusions

Early gestational age at infection, maternal ventilatory supports and low birthweight are the main determinants of adverse perinatal outcomes in fetuses with maternal COVID-19 infection. Conversely, the risk of vertical transmission seems negligible.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was approved by the IRB of the University of Naples Federico II (April 2020, approval number: 145/2020).

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