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Perinatal mortality and morbidity of SARS-COV-2 infection during pregnancy in European countries: findings from an international study

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Dear Editor,

after being epidemic in China, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) infection has rapidly spread in many countries as a global pandemic, with the number of affected cases dramatically increasing worldwide on a daily basis. Although the median age of hospitalized patients with confirmed infection is usually more advanced,¹ with older age reported to be associated to higher mortality rate,² physiological adaptations occurring during pregnancy have been claimed to be potentially responsible for a more severe respiratory disease, thus leading to higher rates of maternal and fetal complications.³⁻⁴

Evidence has been accumulating rapidly in the last months to provide early information to help with counseling and care of pregnant women with SARS CoV-2 infection, and despite the relatively short time from the pandemic outbreak, a multitude of systematic reviews have been published on the topic of SARS-COV-2 infection and COVID-19 disease during pregnancy. However, these studies often share important limitations that might affect the robustness of the results.^{1,3-6}

Since Europe is currently handling the real possibility of a “second wave”, with a new, daily, progressive increase in the number of infected patients after governments’ mitigation policies to minimize the virus transmission, there are still several outstanding issues that should be settled soon to guide the antenatal counselling and management of women with COVID-19 during pregnancy.

Here we present a secondary analysis on perinatal mortality and morbidity in European compared with non-European pregnant women involved in one of the largest retrospective cohort studies on COVID-19 during pregnancy.⁷⁻⁸ This was a multinational, retrospective cohort study that included all pregnant women with a laboratory-confirmed SARS-COV-2 infection, diagnosed between February 1, 2020 and April 30, 2020, in 72 centers from 22 different countries in Europe, Asia, North and South America and Australia (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).⁷ All infected women were diagnosed antepartum during pregnancy, on the basis of The World Health Organization (WHO) interim guidance⁹ (a confirmed case of SARS-COV-2 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction assay of nasal and pharyngeal swab specimens).¹⁰⁻¹¹ Neonates from mother positive to SARS-COV-2 were usually tested within 24 hours after delivery with RT-PCR assay of nasal and pharyngeal swab (Table 1).

The findings from this secondary analysis focused on regional differences shows that in European countries the rate of stillbirth was significantly lower, compared with non-European countries (1.0% vs 7.4%, OR: 0.12, $p = 0.02$), while the rate of neonatal death was similar when evaluating only pregnancies with live-born. In these subset of pregnancies, the rate of admission in neonatal intensive care unit (NICU) was significantly lower in European compared with non-European countries (23.9% vs 42.0%, OR: 0.43, $p = 0.01$). Finally, there was no difference between European and non-European countries in terms of intrauterine growth restriction, preterm birth before 37 weeks of gestation, possible vertical transmission and low birth weight (Table 2).

Thus, pregnant women infected with SARS-COV-2 had better perinatal outcomes in European compared with non-European countries, despite being significantly older and having a significantly higher rate of pre-existing chronic diseases. However, gestational age at infection was significantly higher in European women. In this scenario, the lack of data in literature on SARS-COV-2 infection during the first and early second trimester does not allow to ascertain whether a seroconversion occurring early in pregnancy may increase the risk of adverse perinatal outcomes. It is also entirely possible that different income level of countries and healthcare systems, heterogeneity in the management of both the mother and the fetus, and different criteria for NICU admission might have independently affected perinatal outcomes. Finally, some of the centers included belong to countries that have been seriously hit by the pandemic and whose health systems have been overwhelmed, which may also have influenced the results.

Thus, future analyses on COVID-19 during pregnancy should aim at reporting the course of the disease when the infection is contracted in early pregnancy, the most appropriate type and frequency of fetal monitoring, and antenatal and perinatal risk factors in order to create multiparametric risk score models to predict fetal and maternal adverse outcomes both at diagnosis of infection and at delivery.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Characteristics of the included women

	European countries (n=203)	Non-European countries (n=54)	p value
Mean age in years \pm SD	33.1 (4.8)	29.5 (5.2)	< 0.0001
Mean gestational age at infection (weeks) \pm SD	35.3 (4.1)	33.4 (5.5)	0.005
Smoking	32 (15.8)	3 (5.5)	0.06
Chronic disease pre-existing pregnancy*	95 (46.8)	13 (24.1)	0.003
Obesity**	21 (10.3)	2 (3.7)	0.15
Any symptoms of COVID-19 at diagnosis	149 (73.4)	33 (61.1)	0.08
Hydroxychloroquine	59 (29.1)	1 (1.9)	0.003
Any antibiotics	47 (23.2)	8 (14.8)	0.19
Low molecular weight heparin	43 (21.2)	16 (29.6)	0.19
Any antiviral drug	45 (22.2)	3 (5.5)	0.01
Gestational age at delivery Mean \pm SD	37.1 (2.9)	37.7 (2.5)	0.17

Data are presented as number (percentage) or as mean \pm standard deviation (SD)

*including diabetes, hypertension, or asthma

**defined as body mass index of 30 or greater

Table 2. Perinatal outcomes of European versus non-European pregnant women infected with SARS-COV-2.

	European countries		Non-European countries		OR	p value
	n	% (95% CI)	n	% (95% CI)		
<i>Women with completed pregnancies*</i>	203	-	54	-	-	-
Stillbirth	2	1.0 (0.3-3.5)	4	7.4 (2.9-18)	0.12	0.02
IUGR	7	3.5 (1.7-7.0)	3	5.6 (1.9-15.1)	0.60	0.48
Preterm birth < 37 weeks	56	27.6 (21.9-34.1)	13	24.1 (14.6-37.9)	1.20	0.61
Live-born infants	201	99.0 (96.5-99.7)	50	92.6 (82.4-97.1)	8.04	0.02
<i>Women with live-born infants</i>	201	-	50	-	-	-
Possible vertical transmission	1	0.5 (0.1-2.8)	0	0.0 (0.0-7.1)	0.76	0.86
Neonatal death **	3	1.5 (0.5-4.3)	2	4.0 (1.1-13.5)	0.36	0.28
Admission to NICU	48	23.9 (18.5-30.2)	21	42.0 (29.4-55.8)	0.43	0.01
Low birth weight	46	22.9 (17.6-29.2)	5	10.0 (4.4-21.4)	2.67	0.05

IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit

*Miscarriages and termination of pregnancies excluded

**Including only live-born infants with 28 days follow-up