Correspondence

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 ante partum during pregnancy, on the basis of The World Health Organization (WHO) interim guidance [9] (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 h 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 Europe 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 this 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).

Table 1: Characteristics of the included women.

| Characteristics                      | European countries (n = 203) | Non-European countries (n = 54) | p value |
|--------------------------------------|-----------------------------|---------------------------------|---------|
| Mean age in years ± SD               | 33.1 (4.8)                  | 29.5 (5.2)                      | < 0.0001|
| Mean gestational age at infection (weeks) ± 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 ± SD | 37.1 (2.9)                  | 37.7 (2.5)                      | 0.17    |

Data are presented as number (percentage) or as mean ± standard deviation (SD).
* including diabetes, hypertension, or asthma.
** defined as body mass index of 30 or greater.

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

|                           | European countries | Non-European countries |
|---------------------------|--------------------|------------------------|
|                           | n                  | % (95% CI)             | n                      | % (95% CI) | OR | p value |
| Women with completed pregnancies* | 203                | 1.0 (0.3–3.5)          | 54                     | –          | –  | 0.02    |
| Stillbirth                | 2                  | 7.4 (2.9–1.8)          | –                      | 0.12       | –  | 0.02    |
| IUGR                      | 7                  | 5.6 (1.9–15.1)         | –                      | 0.60       | –  | 0.48    |
| Preterm birth < 37 weeks  | 56                 | 24.1 (14.6–37.9)       | –                      | 1.20       | 0.61 |
| Live-born infants         | 201                | 92.6 (82.4–97.1)       | –                      | 8.04       | 0.02 |
| Women with live-born infants | 201              | –                      | –                      | 0.00       | –  | 0.86    |
| Possible vertical transmission | 1               | 0.0 (0.0–71)           | –                      | 0.76       | 0.86 |
| Neonatal death**          | 3                  | 4.0 (1.1–13.5)         | –                      | 0.36       | 0.28 |
| Admission to NICU         | 48                 | 42.0 (29.4–55.8)       | –                      | 0.43       | 0.01 |
| Low birth weight          | 46                 | 10.0 (4.4–21.4)        | –                      | 2.67       | 0.05 |

IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.
* miscarriages and terminations of pregnancies excluded.
** Including only live-born infants with 28 days follow-up.

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 multivariate risk score models to predict fetal and maternal adverse outcomes both at diagnosis of infection and at delivery.

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Declaration of Competing Interest
The authors report no conflict of interest

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