

# COVID-19 in pregnancy: Maintaining clarity with expanding evidence

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The coronavirus disease 2019 (COVID-19) pandemic has led to unparalleled changes in the provision of care to obstetric patients. In spite of rapid scientific advancement, much uncertainty remains about how to care for pregnant women and their infants during the pandemic. In this editorial, we discuss three emerging topics concerning COVID-19 and pregnancy: (1) rapidly evolving guidelines for maternal and neonatal care; (2) mother to fetus transmission of Severe Acute Respiratory Syndrome associated Coronavirus-2 (SARS-CoV-2); and (3) exclusion of pregnant women from randomized trials.

## Rapid evolution in guidelines for maternal and neonatal care

Since declaration of the global pandemic by the World Health Organization (WHO) in March 2020, there has been lack of clarity surrounding recommendations for patient screening and management, and the appropriate use of personal protective equipment (PPE) for healthcare workers. Confusion initially arose because of conflicting advice from major government and professional societies including the WHO, Centers for Disease Control (CDC), Society of Obstetrics and Gynecology of Canada, Society for Maternal Fetal Medicine, and the American College of Obstetrics and Gynecology (ACOG). While guidelines and recommendations continue to evolve, the CDC and ACOG initially recommended use of N95 masks for the second stage of labour and separation of mothers from babies after birth.<sup>1,2</sup> In addition, the Canadian Pediatric Society recommended breastfeeding without consideration of possible mother to baby transmission.<sup>3</sup>

This uncertainty has underscored the importance of developing regional task forces to establish guidelines for obstetric care providers and their patients. Our jurisdiction of Ontario, Canada is one example. The Ministry of Health appointed the Provincial Council for Maternal and Child Health to synthesize evidence to guide care for COVID-19 in pregnancy.<sup>4</sup> The resulting provincial guideline provides best-practice recommendations on PPE, support persons for pregnant women during labour and delivery, care and testing of newborns, and maternal surveillance.<sup>4</sup> In parallel, there has been rapid development of national and international COVID-19 pregnancy registries, including the CANCOVID-Preg in Canada. These databases will be useful to help us better understand maternal and neonatal COVID-19 outcomes.

## Transmission of SARS-CoV-2 from mother to baby

A second issue is whether SARS-CoV-2 virus can pass from mother to fetus in utero. There have been several suspected cases of perinatal transmission of COVID-19 reported in the literature.<sup>5–7</sup> In these cases, SARS-CoV-2 has been detected in nasopharyngeal swabs of newborns,<sup>5,7</sup> and in some cases following birth by caesarian section where the baby was immediately separated from the mother.<sup>6,7</sup>

However, SARS-CoV-2 has also been detected in amniotic fluid, breast milk, and vaginal swabs (although this might represent cross-contamination with maternal feces), which suggests that virus transmission might also occur intrapartum or postpartum.<sup>7,8</sup> Lack of robust maternal and neonatal testing, potential cross-contamination of samples, and questionable operating characteristics of the SARS-CoV-2 diagnostic test, have made it challenging to determine routes of infections and rates of passage of the virus from mother to baby.

Distinguishing true vertical transmission from intrapartum or postpartum passage of infection will be important moving forward to guide care. Immediate and comprehensive testing of SARS-CoV-2 RNA from cord blood, placenta, and neonatal nasopharyngeal swabs could help differentiate modes of transmission. This has important additional implications for both patients and providers. First, it could inform recommendations on breastfeeding. Second, it could guide whether it is necessary to separate mothers from babies immediately after birth. Third, it would help in protecting healthcare workers (e.g., droplet contact vs. airborne precautions, and appropriate use of PPE) during routine care.

## Exclusion of pregnant women from trials

An additional issue is that pregnant women have been excluded from the majority of trials during the COVID-19 pandemic. A recent study demonstrated that less than 2% of COVID-19 trials included pregnant women, and only three involved an intervention that was a drug or supplement.<sup>9</sup> Exclusion of pregnant women from non-obstetric trials is not new. Historically, this has occurred for several reasons, including ethical concerns regarding the fetus, lack of interest from pharmaceutical companies, and prohibitive regulations.<sup>9</sup> During previous epidemics, including H1N1 and Ebola, there was disproportionate morbidity and mortality in pregnant women, and, pregnant women were similarly excluded from most trials.<sup>10</sup>

There are several important issues concerning the exclusion of pregnant women from trials – and particularly those involving drug therapies – during the COVID-19 pandemic. First, and perhaps most obvious, is that if new treatments emerge they will not be rigorously tested in pregnant women. This means that efficacy, and importantly, maternal and fetal safety will be unknown. This in turn might restrict treatments offered to pregnant women. Second, there are physiologic changes that occur in pregnancy that can lead to important pharmacologic considerations when establishing drug dosing. For example, higher drug doses are sometimes needed in pregnancy due to increased renal clearance and cytochrome P450 enzyme induction. Third, several of the key candidate drugs for COVID-19 (e.g., hydroxychloroquine and lopinavir/ritonavir) have favourable safety profiles in pregnancy. The exclusion of pregnant women in trials evaluating these therapies is even more disappointing. Concerns about harm to pregnant women and fetuses will inevitably lead to a lack of understanding of efficacy and safety of potential COVID-19 therapies in pregnancy. In the end, this may lead to more harm than good.

As the pandemic progresses, we hope to gain further clarity on the above issues related to COVID-19 in pregnancy. Of course, there are

many other important issues to consider including ICU management of pregnant women, screening and surveillance of COVID-19 on labour and delivery wards, and safety measures to allow support persons and family to accompany women during birth, to name a few. Research and knowledge translation will require ongoing and substantial international collaboration. We also believe that significant advocacy will be necessary on the part of both patients and care providers to ensure unique maternal and neonatal health issues are included amidst ongoing scientific progress.

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