EDITORIAL

# COVID-19 in Pregnant Women and Their Newborn Infants

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**Pregnant women** have long been recognized as a vulnerable population during infectious disease pandemics.[1] This was recognized in 1918, during the Spanish influenza pandemic, in which 50% of pregnant women who were infected died. Despite the many advances in critical care since then, similar findings were noted during the 2009 H1N1 pandemic, in which pregnant women were disproportionately more likely to have severe illness, require hospitalization and intensive care, and die than their nonpregnant counterparts.[2,3] Similar findings were noted during the more geographically contained novel coronavirus experiences during the past decades, severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus.[4] It is therefore predictable that enhanced risks are associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Related article

In this issue of *JAMA Pediatrics*, Villar and colleagues[4] add considerably to our understanding of the magnitude of the risk to pregnant women, and by extension their newborn infants, from COVID-19. Previous meta-analyses and surveillance studies had from early on identified pregnant women as a vulnerable group who, although in some analyses were less likely to be symptomatic than their nonpregnant counterparts, were more likely to need hospitalization and intensive care once symptoms develop.[5-7] This prospective observational study examining the outcome of SARS-CoV-2 infection in pregnancy is one of the largest reported to date (to my knowledge), and it reports on the experience from 18 different countries in real time as the pandemic evolved from the earliest cases detected and our understanding of the full spectrum of disease attributable to COVID-19 grew.[4] Each pregnant woman diagnosed with SARS-CoV-2 infection was matched with 2 contemporaneous women who were not diagnosed with infection but were of similar gestation. Detailed outcomes on the cases with SARS-CoV-2 infection and their counterparts without infection were compared by their maternal morbidity and mortality index, severe neonatal morbidity index, and severe perinatal morbidity and mortality index. Statistical models were adjusted for potential confounders, such as country of diagnosis, month entering the study (an important variable because knowledge regarding the natural history and clinical manifestations of infection and best practices in management evolved considerably over the course of the study[4]), maternal age, and preexisting maternal morbidity, including conditions known to be associated with poor outcomes in COVID-19.

The results reported are sobering.[4] Although only 59.2% of diagnosed cases were symptomatic, women with infections overall were at significantly higher risk of poor outcomes, such as preeclampsia or eclampsia, severe infections, admission to an intensive care unit, preterm births (both spontaneous and medically indicated), and maternal death. Risks of maternal morbidity and preeclampsia for pregnant women who remained asymptomatic were lower, but they remained higher than those of individuals who were not infected. Unsurprisingly, given the burden of maternal disease, the relative risk for severe neonatal morbidity index and severe perinatal morbidity and mortality index were 2.66 and 2.14, respectively, in pregnant women who were infected compared with those who were not infected. Neonatal outcomes reflected the severity of maternal illness, but somewhat reassuringly, only 12.9% of newborns born to women with infections tested positive for SARS-CoV-2 infection themselves, and there was no evidence that breastfeeding was associated with an increased risk of infection.

How then do we interpret these findings and place them in their proper context? These detailed data are certainly consistent with observations from smaller studies and national surveillance systems in the US and elsewhere.[5-7] They confirm that similar to other respiratory illnesses, such as influenza, pregnant women and their infants have a unique risk of severe disease and poor outcome. Many biological reasons for this observed enhanced risk are obvious.[6] Certainly, the physiologic changes associated with pregnancy, such as increased heart rate and oxygen consumption, decreased lung capacity (which is exaggerated as pregnancy progresses), and an increased risk of thromboembolic events have a role, especially in a disease in which hypercoagulability is described.[1,6] These changes affect maternal morbidity and placental function and integrity, with an inevitable further risk to the fetus and newborn infant. Pregnancy itself represents a natural state of immunosuppression, with a shift away from cell-mediated immunity.[1,6] These biological factors combine and serve as a partial explanation for these observations. However, it is important to recognize that the absolute risks of severe COVID-19 for pregnant women are low, as acknowledged by the American College of Obstetricians and Gynecologists.[7] For context, during the H1N1 influenza pandemic in the US, 5% of pregnant women who were infected died, while pregnant women accounted for only 1% of the general population, and intensive care admissions of pregnant women with infection were 7-fold higher than admissions among those who were not pregnant.[2,3] It is also important to note, as Villar and colleagues do,[4] that while the risk of COVID-19–associated death was 22 times higher in the SARS-CoV-2–infected group, these deaths were concentrated in regions where resources were less readily available, specifically resources associated with intensive care practices.[4] It is

noteworthy that while pregnancy itself is a risk factor, this and other reports stress that other comorbidities associated with poor outcome from COVID-19, such as overweight, preexisting diabetes, hypertension, and chronic respiratory illnesses, and even demographic variables, also play a role.[6-8] In addition, the presence of symptoms and subtypes of clinical symptoms (for example, fever and shortness of breath) may have some value in terms of interventions in the future. Longitudinal study and further research studies are critical in better defining this risk.

The heightened risk of poor outcomes for pregnant women emphasizes the need to optimize prevention strategies for COVID-19. In the US, there are currently 3 COVID-19 vaccines approved under Emergency Use Authorization (EUA) for use in individuals as young as 16 to 18 years, with more vaccines likely to be approved under EUA during the next 12 months.[9-11] These vaccines use a variety of constructs, such as the novel messenger RNA construct, adenovirus vectors, and protein subunit vaccines. Pregnant women were and are excluded from clinical trials of these vaccines, and data are at this time very limited as to pregnancy outcomes and vaccine efficacy in preventing symptomatic disease in pregnant and other vulnerable populations. Reassuringly, no reproductive, fetal, embryonal, or postnatal concerns were identified in animal studies of the current EUA-approved vaccines, and because they are nonreplicating vaccines, expert opinion is that they will not cause illness in a mother or infant.[12] As a result, pregnant women are not excluded from receiving COVID-19 vaccines, although the US Centers for Disease Control and Prevention and American College of Obstetricians and Gynecologists guidance advise this decision is optimally discussed between the pregnant woman and their clinician, although this is not a requirement.[12,13] Factors that affect the decision to vaccinate include the level of transmission of COVID-19 in the community, a pregnant woman's individual risk of acquiring infection, comorbidities that may affect disease severity if a pregnant women is infected, and acknowledgment of the paucity of trial data to inform the decision. Pregnant women who then opt for vaccination are encouraged to enroll in registries and be followed for safety and efficacy. As of March 2021, more than 30 000 pregnant women in the US have received the messenger RNA vaccines and registered with the V-Safe Surveillance System operated by the US Centers for Disease Control and Prevention.[14] Initial safety data are encouraging. Similar rates of local and systemic reactions were seen among pregnant and nonpregnant individuals. Of more than 1800 individuals participating in the pregnancy registry, there have been 275 pregnancy outcomes, and to date, no unexpected pregnancy or infant outcomes have been observed. Further surveillance and longitudinal studies examining not only safety but also the immunogenicity and efficacy are urgently needed to further assess the potential outcomes of COVID-19 vaccine use in pregnancy. This assumes greater importance since the maternal immunization platform is a 2-for-1 strategy with the potential to affect not only maternal morbidity but potentially benefit the infant through the first few months of life.[1]

Traditionally, adoption of the maternal immunization platform has been slow. Despite influenza vaccination being recommended for pregnant women since the 1990s, vaccination rates in pregnancy before the COVID-19 pandemic were approximately 55%,[15] and those for pertussis booster vaccines were also suboptimal.[15] Some pregnant women will likely not feel comfortable getting a COVID-19 vaccine until more data are forthcoming. For these women, adherence to public health guidance regarding mask wearing, handwashing, and social distancing are first and necessary steps, and pregnant women should be counseled about avoiding crowds and activities with high risk of transmission, such as crowded restaurants. Establishing herd immunity through improving community vaccination rates, so that all in contact with pregnant women are less likely to be infected themselves and transmit infection, is another goal if, as is hoped, the EUA vaccines are proven to reduce or prevent transmission.

The novel SARS-CoV-2 virus and COVID-19 pandemic have resulted in a fundamental lifestyle change in all countries. Understanding this infection in vulnerable populations, such as pregnant women and newborn infants, is essential in defining research priorities. The report by Villars and colleagues[4] has contributed greatly to the definition of risks and is an important contribution to allow the recognition of symptoms and clinical syndromes that elevate that risk and in time allow the targeting of therapies and other interventions.

## ARTICLE INFORMATION

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