

Received: 2021.07.01

Accepted: 2021.07.02

Available online: 2021.07.02

Published: 2021.07.05

Editorial: Maternal SARS-CoV-2 Infection and Pregnancy Outcomes from Current Global Study Data

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Abstract

During the global COVID-19 pandemic, data from clinical studies, systematic review, and population registry data have shown that when compared with non-pregnant women, SARS-CoV-2 infection in pregnancy is associated with a small increase in risk to the mother. Large cohort studies and registry data collected from 2020 have included the US Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET), COVI-PREG, the UK and Global Pregnancy and Neonatal Outcomes in COVID-19 (PAN-COVID) study, the American Academy of Pediatrics (AAP) Section on Neonatal-Perinatal Medicine (SONPM) National Perinatal COVID-19 Registry, the Swedish Pregnancy Register, and the Canadian Surveillance of COVID-19 in Pregnancy (CANCOVID-Preg) registry. Recently published data have shown that most maternal infections with SARS-CoV-2 occur during the third trimester and result in a small increase in hospital admission, admission to the intensive care unit (ICU), mechanical ventilation, preterm birth, and increased cesarean sections in mothers infected with SARS-CoV-2. However, currently approved vaccines given in pregnancy result in an immune response to current SARS-CoV-2 variants. Transplacental transmission of SARS-CoV-2 to the fetus can occur, but the immediate and long-term effects on the newborn infant remain unclear. Therefore, women who are pregnant or planning a pregnancy should be managed according to current clinical guidelines with timely vaccination to prevent infection with SARS-CoV-2. This Editorial summarizes what is currently known about maternal SARS-CoV-2 infection and pregnancy outcomes from multinational studies.

Keywords: Editorial • COVID-19 • Treatment Outcome

Since the beginning of the SARS-CoV-2 pandemic in early 2020, there have been concerns that pregnant women may have more severe COVID-19 symptoms and negative effects on pregnancy outcomes and that SARS-CoV-2 may be transmitted from the mother to the fetus or newborn infant. A year ago, in July 2020, a systematic review of the literature on SARS-CoV-2 infection in pregnancy concluded that the risk of preterm birth and cesarean delivery increased but that maternal morbidity and mortality were similar to non-infected pregnant women [1]. It was believed that vertical transmission of SARS-CoV-2 'probably' occurred, but only in a small proportion of cases [1]. By September 2020, studies from Italy that examined placental tissue confirmed maternal-fetal transmission of SARS-CoV-2, by recruiting maternal inflammatory cells in the placenta, but without villitis [2,3]. Although vertical transmission of SARS-CoV-2 is rare, it most commonly occurs in the third trimester of pregnancy [2,3].

In April 2021, the findings from the multinational INTERCOVID study were published [4]. This cohort study analyzed data from March to October 2020 from 43 institutions in 18 countries to compare pregnancy outcomes in women infected

with SARS-CoV-2 with non-infected pregnant women who received the same level of maternal care [4]. Pregnant women with COVID-19 had an increased risk for preeclampsia/eclampsia, infections, ICU admission, maternal mortality, and preterm birth [4]. In May 2021, a review of the published literature from April to August 2020 showed that 11% of pregnant women with COVID-19 required admission to the intensive care unit (ICU), 8% required mechanical ventilation, and most maternal infections occurred in the third trimester of pregnancy [5]. Also, this literature review identified that for women with COVID-19 who gave birth, 28% had a preterm birth, and 57% had a cesarean section [5].

Recent studies from population registries have been of particular value in evaluating the epidemiology of SARS-CoV-2 infection in pregnant women. Population registries can provide continuous epidemiological and clinical information on emerging and developing diseases and have previously been a valuable resource for information on maternal and infant disease to improve public health [6]. Several international registries have been established to monitor the effects of COVID-19 in pregnancy. Between March and October 2020, US public health

jurisdictions information was reported to the US Centers for Disease Control and Prevention (CDC), including on pregnancy status and confirmed and probable COVID-19 cases through the national Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET) [7]. A recent modification of the Zika virus international web registry has been developed, COVI-PREG, which collects data on COVID-19 in pregnancy [8]. The impact of COVID-19 on coagulopathy and thrombosis is being assessed from the International Society on Thrombosis and Haemostasis (ISTH) COV-PREG-COAG Registry [9].

The UK and Global Pregnancy and Neonatal Outcomes in COVID-19 (PAN-COVID) study included a dataset of outcome data that focused on the effect of SARS-CoV-2 infection on the risk of fetal growth restriction (FGR), miscarriage, stillbirth, pre-term delivery, vertical transmission, and early-onset symptomatic neonatal SARS-CoV-2 infection [10]. The American Academy of Pediatrics (AAP) Section on Neonatal-Perinatal Medicine (SONPM) National Perinatal COVID-19 Registry includes data for pregnant women who have tested positive for SARS-CoV-2 in samples taken from 14 days before delivery to three days after delivery [10]. In April 2021, Mullins et al. reported the findings from the 2020 UK PAN-COVID registry, which included pregnancies with maternal SARS-CoV-2 infection and the US AAP-SONPM National Perinatal COVID-19 registry which included data on SARS-CoV-2-pregnancies and maternal, fetal, perinatal, and neonatal outcomes [11]. The findings from 4,005 pregnant women with SARS-CoV-2 infection, 1,606 cases from PAN-COVID, and 2,399 cases from AAP-SONPM showed a maternal mortality rate of 0.2-0.5%, early neonatal death in between 0.2-0.3%, and stillbirth in 0.4-0.6% of births, with pre-term delivery at <37 weeks gestation in between 12.0-15.7% and extreme preterm delivery at <27 weeks gestation in between 0.3-0.5% [11]. Neonatal SARS-CoV-2 infection was reported in between 0.9-1.8% of all deliveries, and the rates of neonatal small for gestational age (SGA) were between 8.2-9.7% [11]. The high concordance in the findings from the two registries from the UK and US, PAN-COVID and AAP-SONPM, supports the need for public health guidelines to prevent SARS-CoV-2 infection and to promote vaccination of pregnant women and women who are planning a pregnancy.

In May 2021, the findings from national registry data from a prospective cohort study from Sweden were published to determine the outcomes for infants born to mothers who tested positive for SARS-CoV-2 infection [12]. The investigators linked and analyzed the Swedish Pregnancy Register, the Register for Communicable Diseases, and the Neonatal Quality Register that contained 92% of all live births in Sweden between March, 2020 and January, 2021 [12]. However, the authors regarded the findings as exploratory only, as maternal SARS-CoV-2 infection in pregnancy was only significantly associated with a small increase in some neonatal morbidities [12]. Of the 88,159

infants born during the study period, 2,323 (1.6%) were delivered to mothers who were SARS-CoV-2-positive [12]. The mean gestational age of infants born to SARS-CoV-2-positive mothers was 39.2 weeks compared with 39.6 weeks for infants born to non-infected mothers [12]. After matching for maternal characteristics, there was an increase in admissions to NICU (11.7% versus 8.4%), neonatal respiratory distress syndrome (1.2% versus 0.5%), and hyperbilirubinemia (3.6% versus 2.5%) [12]. Neonatal mortality of infants born to SARS-CoV-2-positive mothers was 0.30% compared with 0.12% for infants born to non-infected mothers [12]. Only 21 infants (0.90%) of SARS-CoV-2-positive mothers had positive tests for SARS-CoV-2 in the neonatal period, 12 infants had no neonatal morbidity, and none had congenital pneumonia [12].

On June 3rd, 2021, data were published from the Canadian Surveillance of COVID-19 in Pregnancy (CANCOVID-Preg) registry from five provinces in Canada, including British Columbia, Ontario, Manitoba, Quebec, and Alberta [13,14]. There were 4,805 pregnant women included in the CANCOVID-Preg registry as of March 31st, 2021 [13,14]. Data from this registry showed that 37.5% of SARS-CoV-2-positive pregnant women were between 30-34 years of age, 40.1% were diagnosed at between 14-27 weeks gestation, and 43.7% of cases had community-acquired SARS-CoV-2 infections [13,14]. Obesity was the most common co-morbidity in 12.9%, followed by diabetes in 11.2%, and cardiovascular disease in 3.3% [14]. The most common symptoms of COVID-19 in pregnancy were cough (38.5%), fever (27.1%), and headache (25.6%), but 8% were asymptomatic [14]. This study showed that 7.1% of women were hospitalized, and 2.8% required admission to the ICU [14]. Comparison with non-pregnant women of between 18-45 years with COVID-19 showed that pregnant women with COVID-19 were at increased risk of hospitalization (RR 4.26; 95% CI, 3.45-5.10), and admission to the ICU (RR 2.68; 95% CI, 2.02-3.40) [14]. The pregnancy outcomes included 97.4% live births, 87.1% of deliveries occurred at term, and 12.9% were preterm deliveries [14]. Most of the infants (82.6%) had an average birth weight (range, 2,500-4,000 gm), but 15.2% required admission to the NICU [14]. In this Canadian population study, stillbirth rates were 10.6 per 1,000 (95% CI, 6.6-16.8) compared with 5.44 per 1,000 in the general population (95% CI, 5.1-5.7), which means that although the stillbirth rates for pregnant women with COVID-19 were slightly above the general population, the absolute numbers are small [13,14]. A concern highlighted by this registry study was that not all newborn infants were tested for SARS-CoV-2 infection, which means that data on the infection rates in newborn infants was unknown [13,14].

New variants of SARS-CoV-2 have been identified that show different transmission and clinical outcomes [15]. There are still questions regarding whether any of the variants of concern

of SARS-CoV-2 have more severe effects on the mother, fetus, and newborn infant. However, early studies have shown that approved vaccines for SARS-CoV-2 effectively prevent infection due to the current main variants of concern of SARS-CoV-2 [16]. A recent exploratory study showed that mRNA vaccines were immunogenic in pregnant women and that antibodies were transported to the infant cord blood and were present in maternal breast milk [17]. Also, pregnant women and non-pregnant women vaccinated with approved mRNA vaccines developed cross-reactive antibody responses and T-cell responses against current SARS-CoV-2 variants of concern [17].

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Conclusions

Data from clinical studies, systematic review, and population registry data have shown a small increase in risk to the mother from SARS-CoV-2 infection. Transplacental transmission of SARS-CoV-2 from the mother to the fetus can occur, but the immediate and long-term effects on the newborn infant remain unclear. The increased risk of hospitalization and ICU admission in pregnant women infected with SARS-CoV-2 may be due to the immunosuppressive effects of pregnancy or increased caution by healthcare providers during the COVID-19 pandemic. Women who are pregnant or planning a pregnancy should be managed according to current clinical guidelines with timely vaccination to prevent infection with SARS-CoV-2.