Hong Kong J Gynaecol Obstet Midwifery 2023;23(1):63-72 | https://doi.org/10.12809/hkjgom.23.1.10

Pregnancy outcomes after SARS-CoV-2 infection: the current evidence

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Many questions have been raised about SARS-CoV-2 infection complicating pregnancy such as whether pregnancy increases the susceptibility to SARS-CoV-2 infection, whether SARS-CoV-2 infection in pregnancy is associated with more severe disease and higher mortality, and whether SARS CoV-2 infection during various stages of pregnancy is associated with increased risks of adverse pregnancy and neonatal outcomes. Moreover, there are controversies on the association between SARS-CoV-2 infection and the development of pregnancy complications such as pre-eclampsia, preterm delivery, and fetal growth restriction. In addition to the direct impact of COVID-19 infection on pregnancy outcomes, social restriction measures and changes in healthcare system during the COVID pandemic are reported to lead to adverse pregnancy outcomes such as increased stillbirths. This review aims to summarise the current evidence in the literature on these issues.

Keywords: COVID-19; Pre-eclampsia; Pregnancy outcome; Preterm birth; SARS-CoV-2

Introduction

Clinical management for pregnant women with SARS-CoV-2 infection should be similar to that for women without pregnancy. The Royal College of Obstetricians and Gynaecologists[1], the National Institutes of Health[2], and the Society for Maternal and Fetal Medicine[3] regularly update their clinical guidelines for management of pregnant patients. Therefore, the management of SARS-CoV-2 infection in pregnancy is not discussed in this review, nor is the safety of COVID vaccines in pregnancy. This review aims to highlight the current evidence in the literature on pregnancy outcomes complicated by SARS-CoV-2 infection.

Does pregnancy increase susceptibility to COVID infection?

The physiological changes during pregnancy may create an immune-compromised state leading to a higher susceptibility to COVID infection during pregnancy. However, comparison between studies may not be feasible because of differences in vaccination rates among pregnant women and in the prevalence of COVID in the community. Data obtained in the early stages of the pandemic before the availability of COVID vaccines are more useful. According to the Centers for Diseases Control and Prevention, the incidence of laboratory-confirmed SARS-CoV-2 infection among women aged 15 to 44 years was 9% for pregnant women and 5% for non-pregnant women[4]. However, the study had a lot of missing data, and the testing and ascertainment rates differed between pregnant and non-pregnant women. The higher infection rate in pregnant women was likely the result of much more widespread screening of pregnant women. In another study in the United States, the infection rate was higher among pregnant women (13.9/1000 deliveries) than non-pregnant women (7.3/1000) aged 20 to 39 years[5]. However, the study was not controlled for various confounders such as exposure risks. Similar to the general population, the incidence of SARS-CoV-2 infection in pregnancy has been reported to be consistently higher among those living in socially and economically disadvantaged settings, those with lower household incomes, those with higher unemployment rates, those of minor ethnic groups, those lacking health insurance, and those in high-density neighbourhood[6,7]. Contrarily, in Hong Kong, people in lower social classes (the working poor and ethnic minorities) were more badly affected economically by the pandemic, but significantly higher infection rates in lower socioeconomic groups were not observed, nor were higher infection rates associated with underprivileged pregnant women[8,9].

Is SARS-CoV-2 infection more severe in pregnancy?

The 2003 SARS outbreak in Hong Kong resulted in three deaths among 12 pregnant women with the infection, giving a mortality rate of 25%[10]. SARS-CoV-2

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infection is of lower mortality than SARS infection but still causes more severe disease in pregnant women than non-pregnant women. In the early stage of the pandemic before vaccination was available, among over 400 000 women of reproductive age with symptomatic SARS-CoV-2 infection adjusted for age, race, ethnicity and underlying medical conditions, pregnant women had a three-fold increase in the risk for intensive care unit (ICU) admission (10.5 vs 3.9 per 1000 cases), 2.9-fold increase in the need for invasive ventilation (2.9 vs 1.1 per 1000 cases), 2.4-fold increase in the need for extracorporeal membrane oxygenation (0.7 vs 0.3 per 1000 cases), and 1.7-fold increase in death from the infection (1.5 vs 1.2 per 1000 cases), compared with non-pregnant women[11]. The increased morbidity and mortality in pregnancy are ascribed to physiological changes (such as decreased tidal volume as the uterus enlarges, immunological compromises) and increased risks for thromboembolism in pregnancy.

Using data from the national registry in Mexico that included admission data from 475 hospitals to compare 5183 pregnant women and 175 905 non-pregnant women of reproductive age (15-45 years) with COVID-19 infection confirmed by real-time reverse-transcription (RT-PCR), the crude rates of death, pneumonia, intubation, and ICU admission were 1.5% and 1.5%, 9.9% and 6.5%, 8.1% and 9.9%, and 13.0% and 6.9%, respectively[12]. After propensity score matching, pregnant women were still at higher risk of death (odds ratio [OR]=1.84), pneumonia (OR=1.86), and ICU admission (OR=1.86). Pregnancy is a risk factor for death and severe morbidity in women of reproductive age with SARS-CoV-2-infection, even after adjusting for demographic and medical factors.

In a multinational study conducted between March and October 2020 involving 706 pregnant women with or without SARS-CoV-2 infection in 43 institutions in 18 countries, women with SARS-CoV-2 infection were at higher risk for hypertensive disorders in pregnancy (relative risk [RR]=1.76), severe infections (RR=3.38), ICU admission (RR=5.04), spontaneous preterm delivery (RR=1.59), iatrogenic preterm delivery (RR=1.97), severe neonatal morbidity (RR=2.66), severe perinatal morbidity and mortality (RR=2.14), and maternal mortality (RR=22.3)[13]. Fever and shortness of breath was associated with increased risks of severe maternal complications (RR=2.56) and neonatal complications (RR=4.97), whereas asymptomatic women with COVID-19 infection were at higher risk for maternal morbidity (RR=1.24) and preeclampsia (RR=1.63) only. SARS-CoV-2 infection in pregnancy was associated with consistent and significant increases in severe maternal and neonatal morbidity and mortality.

In the CANCOVID-Preg study in Canada comparing 6012 pregnant women from six provinces with positive polymerase chain reaction (PCR) for SARS-CoV-2 and two age-matched control groups of uninfected pregnant women and non-pregnant women with SARS-CoV-2 infection between March 2020 and October 2021, pregnant women with infection were associated with an increased risk of SARS-CoV-2–related hospitalisation (7.75% vs 2.93%, RR=2.65) and ICU admission (2.01% vs 0.37%, RR=5.46), compared with non-pregnant women with infection[14]. Worse pregnancy outcomes were associated with increasing age, pre-existing hypertension, and more advanced gestation at diagnosis. Pregnant women with infection were at higher risk of preterm delivery (11.05% vs 6.76%, RR=1.63) even when hospitalisation was not needed, compared with uninfected pregnant women.

In a meta-analysis of 435 studies, 9% of pregnant or recently pregnant women attending or admitted to hospital for any reason were diagnosed as having SARS-CoV-2 infection[15]. The most common clinical manifestations were fever and cough (both around 36%). The risks of ICU admission (OR=2.61) and mechanical ventilation (OR=2.41) were higher in pregnant than non-pregnant women. The mortality rate of pregnant women with infection was 0.2% (970/179 981 women in 123 studies). Compared with pregnant women without infection, pregnant women with infection had increased odds of maternal death (OR=6.09), ICU admission (OR=5.41), caesarean section (OR=1.17), and preterm birth (OR=1.57). The odds of stillbirth (OR=1.8) and admission to the neonatal intensive care unit (OR=2.18) were also higher in babies born to women with infection, compared with those without infection. The updated version of this meta-analysis published in May 2022 is by far the largest and most comprehensive evaluation of pregnancy outcome after SARS-CoV-2 infection.

In other studies conducted in 2020 before vaccination was available, pregnant women with SARS-CoV-2 infection were reported to have more adverse outcome[16-20]. However, widespread community vaccination should probably attenuate the morbidity and mortality figures. Although infection is associated with a higher risk in pregnant women compared with non-pregnant women, risk factors for severe disease are similar among both groups. In a study in the United Kingdom, black ethnicity, advanced maternal age, and overweight or obesity were risk

factors for hospital admission among pregnant women[20]. Other studies confirmed that more severe SARS-CoV-2 disease during pregnancy was associated with non-white ethnicity, advanced maternal age, pre-existing medical conditions (obesity, asthma, chronic pulmonary diseases, hypertension, and diabetes mellitus), pregnancy-specific complications (gestational diabetes and pre-eclampsia), need for mechanical ventilation, and maternal death[15-18].

Maternal morbidity in different SARS-CoV-2 variants

In a multicentre study between March 2020 and January 2022, women with SARS-CoV-2 infection were propensity-matched with four control groups without infection during four periods based on the dominant strain of SARS-CoV-2 virus: March to December 2020 (wild type), January to June 2021 (Alpha [B.1.1.7]), July to November 2021 (Delta [B.1.617.2]), and December 2021 to January 2022 (Omicron [B.1.1.529]). Compared with 12 504 women without infection, 3129 women with infection had significantly higher rates of severe maternal morbidity events in all periods except for the Omicron period[21]. Compared with controls, the OR for any severe maternal morbidity was 2.74 for the wildtype strain, 2.57 for the Alpha variant, and 7.69 for the Delta variant (p for trend <0.01) but was not significant for the Omicron variant (OR=1.21). This trend was similar for respiratory and non-respiratory severe maternal morbidity. The Delta variant was associated with highest rates of maternal morbidity than other variants.

In a study of 1286 unvaccinated pregnant women in Turkey and the United Kingdom who were positive for SARS-CoV-2 by RT-PCR from April 2020 to February 2022 (870 during pre-Delta period, 339 during the Delta period, and 77 during the Omicron period), compared with infection during the pre-Delta period, infection during the Delta period was associated with increased need for nasal oxygen support (RR=2.53), high-flow oxygen or continuous positive airway pressure (RR=2.50), mechanical ventilation (RR=4.20), and extracorporeal membrane oxygenation (RR=11.0), as well as 3.6 times higher maternal mortality rate (5.3% vs 1.5%, p=0.01)[22]. However, the Omicron and pre-Delta periods showed similar rates for nasal oxygen treatment (RR=0.62), high-flow oxygen or continuous positive airway pressure (RR=1.07), artificial ventilation (RR=0.44), and maternal mortality rates (1.3% vs 1.3%, p=0.99). The need for nasal oxygen (RR=0.26) and preterm delivery before 34 weeks (15.4% vs 4.9%, p<0.001) were lower during the Omicron and pre-Delta periods than during the Delta period. This study included only unvaccinated pregnant women so that the full impact of different strains of SARS-CoV-2 could be compared. The results showed that the Delta strain was associated with higher maternal morbidity and mortality, whereas the Omicron and pre-Delta strains resulted in similar disease severity.

Transmission of SARS-CoV-2 to fetus

SARS-CoV-2 can transmit to the fetus as an intrauterine infection, an intrapartum infection (during labour and delivery), or a postpartum infection of the neonate (through breast feeding or close contact). However, only a few cases of intrauterine infection have been reported[23,24], whereas postpartum infection is the most common. Despite the risks of postnatal transmission, it is probably safe for an infected mother to continue to breastfeed, because replication competent virus has not been detected in breast milk although breast milk is positive for SARS-CoV-2 by PCR[25,26]. In a cohort of 1481 deliveries in New York, 8% of the mothers were tested positive for SARS-CoV-2[27]. The mothers were allowed to breastfeed provided that they consistently used surgical masks and practised hand hygiene and breast cleansing. All babies had negative PCR results at 5 to 7 days and 14 days of life. Therefore, perinatal transmission is unlikely if adequate hygiene measures are instituted. Direct breastfeeding should be safe when sufficient instructions on infant protection were given to parents.

In a meta-analysis of 206 cohort studies and 266 case series and case reports, 1.8% of 14 271 babies were born to mothers with SARS-CoV-2 infection by RT-PCR[28]. Of 592 babies positive for SARS-CoV-2 with exposure time and type, 14 were confirmed to have mother-to-child transmission: seven (of 448 cases) were in utero transmission, two (of 18 cases) were intrapartum transmission, and five (of 70 cases) were early postnatal transmission. Neonates positive for SARS-CoV-2 were associated with severe maternal infection (OR=2.4), maternal death (OR=14.1), maternal admission to ICU (OR=3.5), and maternal postnatal infection (OR=5.0). The data showed that vertical transmission of SARS-CoV-2 is rare but possible. The severity of maternal SARS-CoV-2 infection is the key risk factor associated with SARS-CoV-2 positivity in neonates.

In a meta-analysis of 176 cases of neonatal SARS-CoV-2 infections (confirmed by at least one positive nasopharyngeal swab and/or the presence of specific IgM), 70% and 30% of infections were due to environmental and vertical transmission, respectively[29]. 55% of infected

neonates developed symptoms including fever (44%), gastrointestinal symptoms (36%), respiratory symptoms (52%), neurological symptoms (18%), and abnormal lung imaging (64%). Late infection was associated with a lack of mother-neonate separation from birth (adjusted OR [aOR]=6.6, p<0.0001) but not with breastfeeding (aOR=2.2, p=0.148). Therefore, the risks of neonatal infection should be weighed against the benefits of breastfeeding and mother-infant bonding. Most guidelines support rooming in of the newborn with infected mother, particularly when the mother is afebrile and asymptomatic[1,2,30].

Gestation at the time of infection and obstetric complications

SARS-CoV-2 infection has been reported to be associated with various obstetric complications including preterm delivery, pre-eclampsia, fetal growth restriction, and postpartum haemorrhage[13-16]. However, impact of infection on different gestation stages remains controversial. In a multicentre study of 22483 women of whom 7.4% were tested positive for SARS-CoV-2 infection, women with infection were at an increased risk for severe obstetrical haemorrhage (1.1% vs 0.5%, aOR=1.78), pulmonary morbidity (2.0% vs 0.5%, aOR=3.90), and ICU admission (1.8% vs 0.5%, aOR=3.29), compared with women without infection[31]. However, the timing of infection (whether active or resolved at time of delivery) was not associated with the risk for severe obstetrical haemorrhage or hypertension-associated or neurologic morbidity.

In a multicentre study in the United States in 2020, among 2326 women tested positive for SARS-CoV-2 during pregnancy, 402 who were positive before 28 weeks of gestation had an increased risk of fetal or neonatal death (2.9% vs 1.5%, aRR=1.97), preterm birth at <37 weeks of gestation (19.6% vs 13.8%, aRR=1.29), and hypertensive disorders of pregnancy with delivery at <37 weeks of gestation (7.2% vs 4.1%, aRR=1.74), compared with 11705 women without infection[32]. Nonetheless, there was no difference in the rates of preterm birth at <34 weeks of gestation, any major congenital malformation, small or large for gestational age, and gestational hypertension or preeclampsia with severe features. The incidence of antenatal complications was similar between infections in the first and second trimesters and infections in the third trimester.

In a study in Italy, sero-molecular testing for SARS-CoV-2 at 12, 16, 21 weeks and at delivery identified 10.3% of women who were positive in the first trimester[33]. Composite adverse obstetric outcome was observed in 6.2% of positive women and 10.5% of negative women, whereas composite adverse neonatal outcome was noted in 12.5% of positive women and 7.6% of negative women. In newborns of women who developed IgG antibodies, the same antibodies were detected in arterial cord blood despite neonatal nasopharyngeal swab being negative. No maternal pneumonia or hospital admission secondary to COVID infection were recorded. Asymptomatic or mildly symptomatic women during the first trimester of pregnancy did not experience significantly more adverse events than negative women.

In a study in Turkey, 167 hospitalised pregnant women with confirmed COVID-19 infection were divided into three groups according to the trimester in which infection was diagnosed[34]. Of the women, 29.3% had an active infection at the time of delivery and 70.7% cleared of infection before giving birth. The three gestation groups were comparable in terms of the incidence of preterm birth (p=0.271), preeclampsia (p=0.394), fetal growth restriction (p=0.403), HELLP syndrome (p=0.763), and gestational diabetes mellitus (p=0.664). Four (2.39%) patients required ICU care and one patient died. The gestational age at the time of COVID-19 infection was not correlated with the frequency of adverse pregnancy outcomes among hospitalised pregnant women with severe disease.

Few studies have evaluated the pregnancy complications in women with active SARS-CoV-2 infection at the time of labour and delivery. In a study comparing 84 women who had active infection at the time of delivery and 92 women who had recovered for at least 10 days, the two groups were comparable in terms of the mean gestational age at delivery (39 weeks for both), the overall rate of caesarean delivery (26.2% vs 17.4%), and non-elective caesarean delivery (10.71% vs 4.34%)[35]. In the active-infection group, the rate of severe disease was 2.4% and the rate of critical disease (with ICU admission, mechanical ventilation, and extracorporeal membrane oxygen) was 3.6%, compared with 0% for both in the recovered group. The two groups were comparable in terms of adverse perinatal outcomes. Thus, delivery is safe in women with active infection despite a non-significant trend for more severe disease.

In the multicentre PregOuTCOV study to determine the effect of gestational age at time of infection on obstetric and neonatal outcomes, among 10 925 singleton pregnancies, 393 (3.60%) were infected with SARS CoV-2, of whom 11.7% developed pneumonia and 4% developed acute respiratory distress syndrome[36]. The infected group

had significant increases in composite adverse obstetric outcomes at >20 weeks' gestation (22.75% vs 19.25%, p<0.001) and composite adverse neonatal outcomes at >26 weeks' gestation (17.86% vs 14.28%, p<0.001) after adjusting for confounders. In Cox regression models, those with composite adverse obstetric outcomes were more likely to be infected after 20 weeks gestation (p<0.001), whereas those with composite adverse neonatal outcomes were more likely to be infected after 26 weeks gestation (p<0.001). The incidence of preeclampsia, eclampsia, and HELLP syndrome increased significantly (p=0.002) when infection was at >15 weeks gestation. The incidence of spontaneous preterm delivery at <37 weeks increased significantly (p<0.001) when infection was at >26 weeks. The incidence of preterm delivery at <32 weeks increased significantly (p<0.001) when infection was at >26 weeks. The incidence of NICU admission increased significantly (p<0.001) when infection was at >28 weeks. The incidence of respiratory distress increased significantly (p<0.001) when infection was at >28 weeks. Although the birthweight in the infected group was significantly lower (3129 vs 3228 g, p<0.001), the z-scores of birthweight in the two groups were similar. Although the effect of gestational age at the time of infection on adverse pregnancy outcomes remains controversial, there is a trend for more severe complications when the infection was acquired in the third trimester, compared with earlier trimesters.

Association of infection with pre-eclampsia, preterm delivery, and fetal growth restriction

Epidemiological studies have demonstrated an increased incidence of pre-eclampsia in women with SARS-CoV-2 infection[13,15,16]. In a systematic review and meta-analysis of 42 studies involving over 438 548 pregnant women, SARS-CoV-2 infection was positively associated with preeclampsia (OR=1.33)[37]. Compared with mild infection, severe infection was strongly associated with preeclampsia (OR=4.16), preterm birth (OR=4.29), gestational diabetes (OR=1.99), and low birth weight (OR=1.89).

In a systematic review and meta-analysis of 28 studies comprising 790 954 pregnant women, 15 524 (1.96%) of them were diagnosed with SARS-CoV-2 infection[38]. Infection during pregnancy increased the odds of preeclampsia (pooled aOR=1.58, p<0.0001, 11 studies). Pregnant women with infection had increased odds of preeclampsia severe features (pooled aOR=1.76, 7 studies), eclampsia (pooled aOR=1.97, 3 studies), and HELLP syndrome (pooled aOR=2.10, 1 study), compared with those without infection. Both asymptomatic and symptomatic infections significantly increased the odds of developing preeclampsia, with odds higher in symptomatic patients (OR=2.11) than asymptomatic patients (OR=1.59). However, the meta-analysis was dominated by two large cross-sectional studies (one from the United Kingdom[39] and the other from the United States[40]). The former study included white (76.3%), Asian (12.2%), and black (4.6%) pregnant women; association between infection and pre-eclampsia persisted even after adjusting for maternal age, ethnicity, parity, pre-existing diabetes mellitus, pre-existing hypertension, and socioeconomic deprivation (by the index of multiple deprivation 2019)[41].

Based on these findings, it is recommended that obstetricians should be aware of this and closely monitor pregnant women with infection for early detection of preeclampsia. However, this association was not consistently seen[42,43], and biases have been identified. For instance, in the absence of prospective cohort studies of pregnant women with and without infection to evaluate subsequent development of pre-eclampsia, there is likely to be under-reporting of women who had infection but were relatively asymptomatic and did not go on to develop pre-eclampsia. In addition, most studies made the diagnosis of SARS-CoV-2 infection in the third trimester. Given that the pathophysiology of pre-eclampsia is supposed to originate in the first and early second trimesters, any causal relationship with infection would be more readily established with those having infection at earlier gestational ages. Therefore, the current evidence does not support such a temporal relationship between infection and pre-eclampsia. Moreover, the 1.5 times increased risk of pre-eclampsia in pregnant women with infection (compared with those without infection) is too small to prove causal relationship. Epidemiologically, it should be explained by other underlying confounding or contributing factors. Furthermore, the direct pathophysiology for SARS-CoV-2 infection to pre-eclampsia is still unknown. Possible mechanisms including downregulation of the angiotensin-converting enzyme 2 receptor ACE2 in the placenta by SARS-CoV-2 spike proteins, and upregulation of sFlt-1 and endoglin and other antiangiogenic factors that cause vasoconstriction remains to be proven[41].

The association of SARS-CoV-2 infection with preterm birth is less consistent, compared to pre-eclampsia. Studies of preterm delivery often did not specify the gestation at infection or the difference between spontaneous or iatrogenic preterm births. In a study of 5893 women from 77 countries with pregnancy gestation beyond 20 weeks,

symptomatic SARS-CoV-2 infection before 20 weeks did not increase the risk of preterm delivery, compared with no infection or mild infection after 20 weeks. However, severe infection in late pregnancy significantly increased the risk of preterm delivery (compared with no infection), primarily due to an increase in medically indicated preterm deliveries (including preterm caesarean sections) while the increase in spontaneous preterm delivery was mild. Overall, mild or moderate infection conferred minimal risk, as did severe disease in early pregnancy[44].

Although medically indicated preterm birth appears to be a logical sequalae of severe SARS-CoV-2 infection in the third trimester, the association of earlier infection in the first or second trimester to subsequent preterm birth remains controversial. In the registry of the Maccabi Healthcare Services of Israel, 2753 pregnant women with infection between February 2020 and July 2021 were identified and matched with non-infected pregnant women according to age, last menstruation date, sector, and socioeconomic status[45]. 17.4% and 48.4% of pregnant women were infected during the first and third trimesters, respectively. Infection during the first and second trimester was not associated with preterm labour ($p>0.8$), whereas infection during the third trimester had a greater risk of preterm birth (aOR=2.76), particularly after 34 weeks of gestation (aOR=7.10). Preterm birth risk was higher in symptomatic third trimester infections (OR=4.28). Pregnancy loss incidence was similar in both groups (aOR=1.16). Only infection during late pregnancy was associated with increased risk of preterm birth, particularly among symptomatic women.

In a study using live births documented by California Vital Statistics between July 2020 and January 2021 (n=240 147), births were classified as very preterm (<32 weeks), preterm (<37 weeks), early term (37-38 weeks), and term (39-44 weeks)[46]. The joint effects of SARS-CoV-2 diagnosis, hypertension, diabetes, and obesity on preterm, and very preterm births were calculated. SARS-CoV-2 diagnosis was associated with an increased risk of very preterm birth (aRR= -1.6), preterm birth (aRR= -1.4), and early term birth (aRR= -1.1), and was associated with elevated risks in women with hypertension, diabetes, and/or obesity. It was argued that in this large population-based study, medical comorbidities were contributed by preterm birth rather than SARS-CoV-2 infection per se.

To determine the real impact of asymptomatic/mild SARS-CoV-2 infection on preterm birth not caused by maternal respiratory failure, a case-control study was conducted to compare a preterm birth group of 102 women and a full-term control group of 127 women in Turin[47]. Only women with spontaneous or medically indicated preterm birth because of placental vascular malperfusion were included. Current or past SARS-CoV-2 infection was determined by nasopharyngeal swab testing and detection of IgM/IgG antibodies in blood samples. There was no significant difference in the cumulative incidence of SARS-CoV-2 between the preterm and term groups (20.5% vs 25.1%), although the preterm group was burdened by a higher prevalence of comorbid risk factors including body mass index of >24.9 kg/m^2, asthma, and chronic hypertension. Logistic regression analysis showed that asymptomatic/mild SARS-CoV-2 infection was not an independent predictor for spontaneous and medically indicated preterm birth secondary to pregnancy-related hypertension and its complications. Thus, women without comorbidities should be reassured that asymptomatic/mild SARS-CoV-2 infection does not increase the risk of preterm delivery. Preterm birth and severe SARS-CoV-9 infection shared common comorbidity risk factors, which may explain the high rate of preterm birth secondary to maternal conditions rather than SARS-CoV-2 infection.

Early epidemiological studies have associated SARS-CoV-2 infection with increased incidences of fetal growth restriction. There have been case reports that link SARS-CoV-2–induced placental infarcts with fetal growth restriction[48]. To compare fetal growth velocity and fetal haemodynamics in pregnancies complicated and in those not complicated by severe acute SARS-CoV-2, 49 consecutive pregnancies complicated by SARS-CoV-2 during the second half of pregnancy was prospectively matched with 98 unaffected women[49]. General baseline and pregnancy characteristics were similar. There were no differences between the two groups at the second and third trimesters in terms of head circumference, abdominal circumference, femur length, and estimated fetal weight z-scores as well as growth velocity of all these body parameters and the pulsatility index of both maternal and fetal Doppler scans throughout gestation. Thus, increased fetal growth surveillance is not supported in pregnancies complicated by SARS-CoV-2[49].

In a Japanese study that reviewed the medical records of infants born and admitted to the neonatal intensive care unit and growth care unit of Shiga University of Medical Science Hospital before the COVID-19 pandemic (April to September 2019) and during the pandemic (April to September 2020), apart from fewer preterm babies, there

were fewer infants born with fetal growth restriction during the pandemic period than the pre-pandemic period (12 vs 31, p=0.0002)[50]. There were no significant differences in any infant or maternal factors associated with fetal growth restriction. It was concluded that there was a paradoxical reduction in the number of infants with fetal growth restriction during the COVID-19 pandemic. Therefore, evidence is not consistent on association of SARS-CoV-2 infection with fetal growth restriction.

Social impact of COVID-19 pandemic on obstetric care

In addition to the direct impacts of SARS-CoV-2 infection on pregnant women and pregnancy outcomes, the pandemic itself has negative impacts on healthcare delivery and accessibility and leads to adverse outcomes even among women not infected with SARS-CoV-2. Particularly in the early stages in 2020, the pandemic had profound impacts on healthcare systems and social economic structure worldwide. Extensive lockdowns, disruption of healthcare services, and fear of attending healthcare facilities might also have brought about adverse effects on patient care.

In a retrospective, multicentre cohort study of perinatal outcomes in Melbourne before and during the COVID-19 lockdown (from March 2020 to March 2021), 24817 births exposed to lockdown were compared to 50017 births before the pandemic[51]. There was a higher risk of preterm stillbirth in the exposed group than the control group (0.26% vs 0.18%, aOR=1.49, p=0.015). There was also a significant reduction in the preterm birth of live infants <37 weeks (5.68% vs 6.07%, aOR=0.93, p=0.02), which was largely mediated by a significant reduction in iatrogenic preterm birth (3.01% vs 3.27%, aOR=0.91, p=0.03) including iatrogenic preterm birth for fetal compromise (1.25% vs 1.51%, aOR=0.82). These observations raised concerns that the pandemic in 2020 may have led to a failure to identify and appropriately care for pregnant women at an increased risk of antepartum stillbirth.

In a similar study on the effect of restriction measures to mitigate SARS-CoV-2 transmission during the pandemic on preterm labour, 3150 women who were exposed to restriction measures during pregnancy and 3175 unexposed controls were compared[52]. Preterm birth before 34 weeks or stillbirth occurred in 3.0% exposed pregnancies and in 4.1% controls (RR=0.74, p=0.021). Preterm birth before 34 weeks occurred in 2.4% of women in the exposed group and in 3.4% of women in the control group (RR=0.71, p=0.022), without evidence of an increase in the rate of stillbirth in the exposed group (0.7% vs 0.9%, RR=0.83, p=0.515). Competing-risks regression analysis showed that the effect of the restriction measures on spontaneous preterm birth was stronger and started earlier than the effect on medically indicated preterm birth. The effect was stronger in women with a previous preterm birth (RR=0.42, p=0.008) than in parous women without a previous preterm birth (RR=0.93, p=0.714) [p for interaction=0.044]. Composite adverse perinatal outcome was less frequent in the lockdown exposed group than in controls (2.1% vs 2.9%, RR=0.73, p=0.042). It was concluded that restriction measures to mitigate SARS-CoV-2 transmission were associated with a reduced rate of preterm birth before 34 weeks, which was mainly due to a lower rate of spontaneous prematurity. The effect was more substantial in women with a previous preterm birth and was not associated with an increased stillbirth rate.

In a study of singleton births in United Kingdom National Health Service hospitals conducted between March 2020 to February 2021 comparing 451727 births during the pandemic and corresponding births 1 year earlier, maternal characteristics were similar in the pre-pandemic and pandemic periods[53]. Stillbirth rates remained similar (0.36% vs 0.37%, p=0.16), but the rates of preterm birth (6.0% vs 6.1%, aOR=0.96, p<0.001) and small for gestational age (5.6% vs 5.8, aOR=0.95, p<0.001) were lower during the pandemic, whereas the rates of obstetric intervention were higher during the pandemic (induction of labour: 40.4% vs 39.1%, aOR=1.04; elective caesarean section: 13.9% vs 12.9%, aOR=1.13; emergency caesarean section: 18.4% vs 17.0%, aOR=1.07; all p<0.001). The small changes in obstetric intervention rates and pregnancy outcomes could be associated with women's behaviour, environmental exposure, changes in maternity practice, and reduced staffing levels. The COVID-19 pandemic was not associated with overall worse pregnancy outcomes, and the overall impact on outcome was small.

In a study in the United Kingdom investigating whether the COVID-19 pandemic affected the decision-to-delivery interval and neonatal outcomes in women who underwent category-1 (crash) caesarean section, 562 patients who underwent emergency caesarean section in the pre-COVID-19 period in seven hospitals were compared with 577 patients who underwent emergency caesarean sections during the COVID-19 pandemic from April 2020 to July 2020[54]. The use of general anaesthesia decreased significantly between the two groups (RR=0.48, p<0.0001). Compared with the pre-COVID group, the COVID group had an increase in median decision-to-delivery interval (26

[18-32] vs 27 [20-33] minutes, p=0.043) and a decrease in the number of caesarean sections meeting the decision-to-delivery interval target of <30 min (66.5% vs 60.5%, p=0.02). However, the incidence of adverse neonatal outcomes was similar in the two groups (24.6% vs 24.0%, p=0.85). Thus, the small increase in decision-to-delivery interval during the COVID-19 pandemic did not adversely affect neonatal outcomes.

In a meta-analysis of 40 studies, significant increase in stillbirth (pooled OR=1.28, 12 studies) and maternal death (OR=1.37, two studies) were identified during the pandemic, compared with pre-pandemic[55]. Preterm births before 37 weeks' gestation were not significantly changed overall (OR=0·94, 15 studies) but were decreased in high-income countries (OR=0.91, 12 studies) where spontaneous preterm birth was also decreased (OR=0.81, two studies). The mean Edinburgh Postnatal Depression Scale scores were higher, which indicated poorer mental health, during the pandemic (pooled mean difference=0.42, three studies), but no overall significant effects were identified for other major parameters such as postpartum haemorrhage and neonatal outcome. Owing to the considerable disparity between high-resource and low-resource settings, there is an urgent need to prioritise safe, accessible, and equitable maternity care during the pandemic. Therefore, the evidence suggesting substantial increase in the rates of stillbirth and preterm birth during the pandemic remains controversial. The increasing vaccination rates in most communities to achieve a reasonable degree of herd immunity and a reduction in severe disease and mortality should mean that extensive lockdown measures can be abolished in most countries. Therefore, major interruptions in healthcare delivery and suspension of services in hospitals seen earlier in the pandemic should not reappear. The impact of the pandemic on the overall provision of obstetric services and thus pregnancy outcome should not be a major concern anymore.

Conclusion

Pregnancy increases the risk of having severe disease after COVID-19 infection, but intrauterine transmission of SARS-CoV-2 is rare. Adverse pregnancy and neonatal outcomes are more common among women with severe SARSCoV-2 during pregnancy, whereas comorbid conditions are the main risk factors for developing severe disease. The association of SARS-CoV-2 with pregnancy complications including pre-eclampsia, preterm birth, and fetal growth restriction remains controversial. The negative effects of the pandemic on obstetric outcome secondary to lockdowns and healthcare disruptions should no longer exist, as most communities have abandoned social restrictions with the alleviation of pressure on healthcare systems. With increasing vaccination rates and herd immunity, predominance of SARS-CoV-2 variants with attenuated virulence, and enhanced treatment modalities, it is anticipated that mortality and morbidity associated with SARS-CoV-2 infection should progressively be mitigated. Nevertheless, we should make every effort to enhance our knowledge about SARS-CoV-2 infection in pregnancy as the virus will likely remain with us for a considerable period of time in future.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, WWK To and CW Kong were not involved in the peer review process of this article.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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