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COVID-19 infection and adverse pregnancy outcomes: a retrospective study

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Objective: To determine whether COVID-19 infection in pregnancy is associated with adverse obstetric and perinatal outcomes.
Methods: We conducted a retrospective cohort study in pregnant women who delivered in the Queen Elizabeth Hospital between 1 February 2022 and 30 April 2022. Outcome measures included adverse maternal outcomes (maternal intensive care unit [ICU] admission), obstetric outcomes (abnormal cardiotocography, mode of delivery, postpartum haemorrhage), and adverse perinatal outcomes (preterm delivery, low Apgar score, low birth weight, neonatal ICU admission, neonatal death). The association between maternal COVID-19 infection status and preterm delivery was evaluated.
Results: Among 481 pregnant women, 136 were infected with or recovered from COVID-19 during pregnancy and 345 were not. COVID-19 infection during pregnancy resulted in higher rates of preterm delivery (adjusted odds ratio=2.30), maternal ICU admission, and neonatal ICU admission.
Conclusion: COVID-19 infection during pregnancy is associated with an increased risk of adverse maternal and perinatal outcomes.

Keywords: COVID-19; Pregnancy outcome; Premature birth

Introduction

COVID-19 infection has a wide range of severity from asymptomatic, mild coryzal symptoms to moderate or severe pneumonia to acute respiratory distress syndrome and septic shock[1,2]. Pregnant women are more susceptible to the infection owing to physiological cardiorespiratory and immunological changes[3]. Most patients have mild-to-moderate disease[4], but pregnant women are at a higher risk of developing severe infection. COVID-19 infection is associated with adverse perinatal outcomes[5].

The Queen Elizabeth Hospital is a tertiary public hospital in Hong Kong with 4000 to 5000 deliveries per year. In 2022, it was converted into a designated hospital for COVID-19 patients in the Kowloon Central Cluster. All COVID-19-positive women receiving antenatal care in hospitals of this cluster were transferred to our hospital, whereas COVID-19-negative women in our hospital were referred to other hospitals according to the patient's preference. Nonetheless, a considerable proportion of COVID-19-negative women stayed and delivered in our hospital. We evaluated the association between COVID-19 infection during pregnancy and adverse maternal, obstetric, and fetal outcomes.

Materials and methods

Medical records of women with a singleton pregnancy delivering in the Queen Elizabeth Hospital between 1 February 2022 and 30 April 2022 were retrieved and retrospectively reviewed. Women with multiple pregnancies, stillbirth, or incomplete data were excluded.

Data collected included maternal age, ethnicity, parity, comorbidities (obesity, diabetes mellitus, chronic hypertension, antiphospholipid syndrome and systemic lupus erythematosus, and chronic renal disease), obstetric history (fetal growth restriction, fetal chromosomal abnormalities, gestational diabetes, and gestational hypertensive disorders), and pregnancy and neonatal outcomes (mode of delivery, maternal intensive care unit [ICU] admission, postpartum haemorrhage, abnormal cardiotocography, preterm delivery before 37 weeks of gestation, abnormal low birth weight <2.5 kg, low Apgar score, neonatal ICU admission, respiratory distress, neonatal jaundice, and neonatal death). Obstetric conditions were defined according to international criteria[6-10].

During the pandemic, all pregnant women admitted to our hospital were screened for COVID-19 using real-

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time reverse transcriptase polymerase chain reaction, except for those who recovered from infection within 90 days. Those with indeterminate results were tested with SAR-COV2 protein receptor-binding domain antibody; those with a positive antibody result were considered to have recovered and were managed on the general ward.

Pregnant women with COVID-19 were kept in negative-pressure isolation wards. A single room with negative pressure was used for vaginal delivery and Caesarean section. All staff taking care of COVID-19 patients wore personal protective equipment, surgical gloves, and N95 respirators.

Those with active COVID-19 infection during pregnancy were monitored for vital signs and oxygen saturation. Complete blood tests were performed. Chest radiography was performed to evaluate any pneumonia after obtaining written consent from the mothers, who were explained of the negligible effect of the radiation dose on fetus[11]. Cardiotocography for fetal heart rate monitoring was performed for a gestational age beyond 28 weeks. Ultrasonography was performed for fetal wellbeing if clinically indicated. Symptomatic treatment and antipyretics were given. Given that COVID-19 predisposes to thromboembolic events[12], pregnant women were offered pharmacological thromboprophylaxis up to 10 days after hospital discharge in accordance with the suggestion of The Royal College of Obstetricians and Gynaecologists[13]. Those who refused or had contraindications to pharmacological thromboprophylaxis were supplied with compression stockings as mechanical prophylaxis. Antiviral treatment such as nirmatrelvir/ritonavir (Paxlovid) or remdesivir (Veklury) was prescribed after an assessment by infectious disease specialists. Antibiotic treatment was given if a secondary bacterial infection was present. Those with severe COVID-19 infection were admitted to the ICU for close observation and treatment.

ICU admission was based on the severity of the COVID-19 infection and the need for organ support or invasive monitoring. Those with severe disease, defined by clinical signs of pneumonia plus tachypnoea or desaturation, were admitted to the ICU because of the need for ventilatory support. Those with sepsis that was not responsive to antibiotics and fluid resuscitation were also admitted to the ICU.

Clinical management included invasive monitoring with arterial line and central line insertion to monitor blood pressure and to guide fluid resuscitation, intravenous remdesivir, and empirical antibiotics (for secondary bacterial infection), and ventilatory support, according to inputs from intensive care and infectious disease specialists.

The timing of delivery depended mainly on the severity of the COVID-19 infection as well as the maternal and fetal conditions. Induction of labour or Caesarean section was offered to those with mild-to-moderate COVID-19 infection, based on standard obstetric indications. For those with severe or critical COVID-19 infection, the delivery decision was made jointly by the obstetrician, intensive care physician, and infectious disease specialist after consideration of gestational age, severity of maternal respiratory compromise and sepsis, and fetal wellbeing. Medically indicated deliveries were not delayed owing to COVID-19-positive status alone.

The COVID-19-positive group included those with a history of or active COVID-19 infection during pregnancy. The COVID-19-negative group included those with no history of COVID-19 infection during pregnancy and a negative COVID-19 result on admission for delivery.

Statistical analyses were performed using SPSS (Windows version 29.0.1; IBM Corp, Armonk [NY], United States). The COVID-positive and -negative groups were compared using the Pearson Chi-squared test and the Fisher's exact test, as appropriate. A p value of <0.05 was considered statistically significant. A multivariate logistic regression was used to evaluate the associations between COVID-19 infection and adverse outcome of preterm delivery, adjusting for confounding variables.

Results

Of 481 women included for analysis, 136 (28.3%) were classified into the COVID-19-positive group who had active COVID-19 (n=76) or were recovered from COVID-19 (n=60) and 345 (71.7%) were classified into the COVID-19-negative group (Table). The two groups were comparable in terms of demographics, maternal comorbidities, and current obstetric history, except that the proportion of multiparous women was higher in the COVID-19-positive group.

COVID-19 infection status was associated with maternal ICU admission, preterm delivery, neonatal ICU admission, and respiratory distress, but not associated with obstetric outcomes and rates of instrumental delivery and Caesarean section. In multivariate logistic regression, COVID-19 infection was predictive of preterm delivery

Table. Comparison of COVID-19-positive and -negative groups

Characteristic	COVID-19 positive (n=136)*	COVID-19 negative (n=345)*	p Value
Age, y			0.168
<35	98 (72.1)	226 (65.5)	
≥35	38 (27.9)	119 (34.5)	
Ethnicity			0.636
Asian	134 (98.5)	340 (98.6)	
Non-Asian	2 (1.5)	5 (1.4)	
Parity			0.003
Nulliparous	49 (36.0)	177 (51.3)	
Multiparous	87 (64.0)	168 (48.7)	
Obesity (body mass index ≥30 kg/m^2)	10 (7.4)	18 (5.3)	0.320
Pre-existing diabetes	2 (1.5)	2 (0.6)	0.318
Pre-existing hypertension	0	4 (1.2)	0.263
Systemic lupus erythematosus and antiphospholipid syndrome	1 (0.7)	0	0.283
Chronic renal disease	0	0	-
Gestational diabetes	11 (8.1)	41 (11.9)	0.227
Gestational hypertension	4 (2.9)	4 (1.2)	0.162
Pre-eclampsia	3 (2.2)	9 (2.6)	0.546
Fetal growth restriction	10 (7.4)	22 (6.4)	0.699
Fetal chromosomal abnormalities	2 (1.5)	4 (1.2)	0.543
Abnormal cardiotocography	13 (9.6)	22 (6.4)	0.226
Spontaneous vaginal delivery	92 (67.6)	230 (66.7)	0.837
Instrumental delivery	6 (4.4)	22 (6.4)	0.407
Caesarean section	38 (27.9)	93 (27.0)	0.827
Postpartum haemorrhage >500 ml	6 (4.4)	28 (8.1)	0.153
Postpartum haemorrhage >1000 ml	1 (0.7)	6 (1.7)	0.366
Thromboembolism	0	0	-
Maternal intensive care unit admission	5 (3.7)	1 (0.3)	0.008
Preterm delivery	16 (11.8)	20 (5.8)	0.025
Spontaneous	8 (5.9)	10 (2.9)	
Iatrogenic	8 (5.9)	10 (2.9)	
Low birth weight <2.5 kg	13 (9.6)	23 (6.7)	0.278
Low Apgar score <7 at 5 min	1 (0.7)	1 (0.3)	0.487
Neonatal intensive care unit admission	98 (72.1)	121 (35.1)	<0.001
Respiratory distress	36 (26.5)	51 (14.8)	0.003
Oxygen required	13 (9.6)	31 (8.9)	0.730
Neonatal jaundice requiring phototherapy	17 (12.5)	38 (11.0)	0.645
Neonatal death	0	0	-

* Data are presented as No. (%) of participants

(adjusted odds ratio [OR]=2.30, 95% confidence interval [CI]=1.13-4.68, p=0.022).

Five women in the COVID-19-positive group were admitted to the ICU owing to pneumonia with desaturation requiring oxygen support (n=2), severe sepsis requiring invasive monitoring (n=1), severe pre-eclampsia requiring intravenous antihypertensives and the HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome (n=1), or severe primary postpartum haemorrhage secondary to uterine atony with disseminated intravascular coagulopathy (n=1). However, only one woman in the COVID-19-negative group was admitted to the ICU owing to severe postpartum haemorrhage secondary to a vaginal haematoma.

Eight women in the COVID-19-positive group had iatrogenic preterm delivery owing to severe COVID infection with pneumonia requiring oxygen support (n=2), preterm prelabour rupture of membrane (n=4), severe pre-eclampsia requiring intravenous antihypertensives and the HELLP syndrome (n=1), or abnormal cardiotocography (n=1).

Discussion

In the present study, more COVID-19-positive women were multiparous, probably because families with more school-age children are at higher risk of exposure to the virus[14], and these families are more likely to employ domestic helpers for childcare.

Pregnant women are at an increased risk of severe COVID-19 infection because of physiological changes in the respiratory system, in which progesterone causes oedema in the respiratory mucosa and the diaphragm is lifted up by the gravid uterus, as well as changes in the immune system to accommodate the fetus[15]. Thus, pregnant women are more susceptible to severe COVID-19 infection and its associated comorbidities. They are more likely to be admitted to the ICU and require ventilation support and extracorporeal membrane oxygenation[16], consistent with the findings of the present study.

Clinical manifestations of COVID-19 infection differ across viral strains. Compared with the wild-type, alpha and delta strains result in significantly higher rates of maternal morbidities and mortalities, whereas the omicron variant was not associated with a significant increase in these outcomes[17]. The COVID-19 vaccination rate was also increased in 2022, compared with the earlier waves of the outbreak. The rates of hospitalisation and critical care admission associated with severe COVID-19 infection are lower in the vaccinated group[18,19]. Thus, no invasive ventilatory support or maternal death occurred in those admitted to the ICU.

In the present study, COVID-19-positive women had a higher risk of preterm delivery. This suggests that COVID-19 has a different mechanism rather than an iatrogenic delivery secondary to maternal diseases[20,21]. Further research is warranted. Although the rate of neonatal ICU admission secondary to respiratory distress was higher in the COVID-19-positive group, all these neonates tested negative. Vertical transmission of COVID-19 infection is uncommon.

In a systemic review and meta-analysis of 42 studies involving 438 548 pregnant women[22], COVID-19 infection during pregnancy is associated with an increased odds of pre-eclampsia (OR=1.33, 95% CI=1.03-1.73), maternal ICU admission (OR=4.78, 95% CI=2.03-11.25), preterm delivery (OR=1.82, 95% CI=1.38-2.39), neonatal ICU admission (OR=3.69, 95% CI=1.39-9.82), and stillbirth (OR=2.11, 95% CI=1.14-3.90). No association with fetal distress, Caesarean section, low birth weight, postpartum haemorrhage, or neonatal death was observed. In the present study, COVID-19 infection was not associated with pre-eclampsia or stillbirth, probably owing to the small sample size.

A designated hospital for patients with COVID-19 enabled prompt diagnosis and management and reduced morbidities. The laboratory could take up a large number of tests and prompt diagnoses. Medical staff were trained to provide care on COVID-19 infection and recognise severe infection. Infectious disease specialists provided input to the care, especially on patients with underlying comorbidities and severe illness. Antiviral medications were in adequate supply for immediate prescription after the diagnosis. Women in the COVID-19-positive group were monitored more frequently for blood pressure, temperature, and oxygen saturation to detect severe infection and a need for organ support. This also enabled earlier diagnosis of pre-eclampsia or gestational hypertension.

The present study has limitations. The sample size was small and the study was retrospective. Some COVID-19-positive cases were self-reported or asymptomatic/undiagnosed. The vaccination status was not investigated; vaccination reduces rates of hospitalisation and critical care admission[19]. The effects of antiviral treatment were not evaluated; antiviral treatment reduces rates of maternal

mortality and preterm delivery[23,24]. Long-term outcomes of the newborns were not investigated.

Conclusion

COVID-19 infection during pregnancy is associated with an increased risk of maternal ICU admission, preterm delivery, respiratory distress, and neonatal ICU admission.

Contributors

Both authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. Both 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 an editor of the journal, KYL was not involved in the peer review process. The other author has disclosed no conflicts of interest.

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Data availability

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

Ethics approval

The study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (Reference: KC/KE-22-0144/ER-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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