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A Registry-Based Observational Study on the Maternal and Fetal Outcomes of COVID-19 Patients in Hong Kong

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Abstract

Objective: To report the clinical maternal and fetal outcomes of pregnant women with coronavirus disease 2019 (COVID-19), along with any associated pregnancy complications, in Hong Kong, China, and to assess the impact of COVID-19 vaccination on these outcomes.

Methods: This prospective registry-based observational study included pregnant women who were recruited through convenient sampling and had a laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection with a cycle threshold (Ct) value result available on admission to eight local hospitals in Hong Kong, China. Data on clinical symptoms, laboratory results, medical treatments, delivery timing and mode, and pregnancy complications were extracted from the Hospital Authority's electronic medical record system. Maternal, fetal, and pregnancy outcomes were compared between unvaccinated pregnant women with COVID-19 and those who had received at least one dose of COVID-19 vaccine before diagnosis. Nonparametric continuous variables and categorical variables were analyzed using the Mann-Whitney *U* test and the Pearson's chi-squared test respectively. A *P* value less than 0.05 was considered statistically significant.

Results: A total of 164 pregnant women were included, of whom 78 (47.56%) were nulliparous. COVID-19 was diagnosed before 28 weeks' gestation in 30 (18.29%), while 134 (81.71%) were diagnosed at or after 28 weeks' gestation. Sixty-two (37.80%) women received at least one dose of COVID-19 vaccine. There were no significant differences between vaccinated and unvaccinated groups in the time interval between COVID-19 diagnosis and delivery, the Ct value, and the gestational age at infection onset or delivery ($P > 0.05$). The majority of women were symptomatic at diagnosis regardless of vaccination status (55 (88.71%) in vaccinated group *vs*. 78 (76.47%) in unvaccinated group ($P = 0.052$). Symptoms did not significantly differ between groups except for cough (62.90% *vs.* 47.06%, $P = 0.049$). The overall rate of severe COVID-19 in pregnant women was low. In total, 5 (3.05%) patients experienced severe COVID-19, with vaccinated patients more likely to receive low molecular weight heparin (LMWH) as part of their treatment (62.90% *vs.* 42.16%, $P = 0.010$). Ninety-two (56.10%) women had a spontaneous vaginal delivery, 7 (4.27%) had an instrumental delivery, and 44 (26.83%) and 21 (12.80%) underwent emergency and elective cesarean sections respectively. For fetal outcomes, 14 (8.48%) babies were born preterm and four (2.65% of nonpreterm babies, $n = 151$) had low birthweight. The median birthweight percentile was 52.18th. There were no statistically significant differences in pregnancy complications or fetal outcomes between vaccinated and unvaccinated groups.

Conclusion: The overall rate of severe COVID-19 in pregnant women was low. COVID-19 vaccination did not significantly impact maternal outcomes, except for the use of LMWH. Additionally, the study found no significant differences in fetal outcomes and pregnancy complications between vaccinated and unvaccinated individuals.

Keywords: COVID-19; Maternal outcomes: Fetal outcomes; Pregnancy complications; Severe COVID-19

Introduction

As our understanding on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved, concerns have arisen regarding its effect on pregnancy. Physiological changes during pregnancy, such as elevated diaphragm, increased oxygen consumption, and edema of the respiratory tract mucosa, make pregnant women more vulnerable to severe respiratory

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infections.[1] Although pregnant women do not appear to be more susceptible to SARS-CoV-2 infection than nonpregnant women,[2] they are at a significantly higher risk of developing severe coronavirus disease 2019 (COVID-19) necessitating intensive care unit (ICU) admissions or the use of invasive ventilation.[3]

SARS-CoV-2 enters cells by binding to the angiotensin converting enzyme 2 (ACE 2) receptors,[4] which are expressed in the syncytiotrophoblast and cytotrophoblast.[5] This provides a plausible mechanism for placental infection and vertical transmission of SARS-CoV-2 to the fetus. Previous research has demonstrated that SARS-CoV-2 infection is associated with an increased risk of adverse pregnancy outcomes for both the pregnant woman and the fetus, including increased risk of preeclampsia, gestational diabetes, preterm birth, stillbirth, fetal distress, and low birth weight.[6] A cohort study in England also indicated that SARS-CoV-2 infections were associated with an increase in the overall rate of cesarean section, the number of emergency cesarean sections for maternal indications and the rate of iatrogenic preterm birth.[7]

The emergence of COVID-19 vaccines marked a pivotal movement in the global fight against the COVID-19 pandemic. In Hong Kong, China, the government officially initiated the COVID-19 vaccination program on 26*th* February 2021, both the Joint Committee on Vaccination and Immunization in the United Kingdom (UK) and the Hong Kong College of Obstetricians and Gynecologists endorsed their use in pregnant and lactating women.[8,9] Since then, additional evidence has become available supporting the efficacy and safety of the COVID-19 vaccines in this population.[10–13]

Unlike many other regions, Hong Kong experienced a unique COVID-19 epidemic, with minimal cases reported for approximately 8 months in 2021. However, this period of low COVID-19 activity did not enable adequate immunization in the population.[14] The circulation of the Alpha, Beta, and Delta variants was limited in the community during the early waves of the epidemic, until the highly transmissible Omicron variant was imported, triggering the fifth wave of the epidemic in December 2021.[14] Notably, the clinical outcomes of the local COVID-19 cases during pregnancy in Hong Kong have not been reported previously.

This study aimed to elucidate the clinical characteristics, and both maternal and fetal outcomes of the pregnant women with SARS-CoV-2 infections during the COVID-19 epidemic in Hong Kong. Additionally, the impact of COVID-19 vaccination on maternal and fetal outcomes was also evaluated.

Methods and material

This prospective, registry-based observational study was conducted between March 27, 2020, and August 27, 2022. Pregnant women were recruited through convenient sampling and included if they had a laboratory-confirmed SARS-CoV-2 infection with a cycle threshold (Ct) value result available on admission to two local tertiary teaching hospitals (Prince of Wales Hospital and Queen Mary Hospital) and six local public hospitals (Queen Elizabeth Hospital, United Christian Hospital, Princess Margaret Hospital, Tuen Mun Hospital, Kwong Wah Hospital, and Pamela Youde Nethersole Hospital). Relevant clinical symptoms, laboratory findings, medical treatments, and outcome data were extracted from a clinical management system, an electronic medical record system designed by the Hospital Authority, Hong Kong.

The date of diagnosis of COVID-19 was defined as the day when there was a positive result by quantitative reverse transcriptase polymerase chain reaction assay of maternal nasal and pharyngeal swab or deep throat saliva specimen. The intervals from diagnosis to delivery were recorded. Patients who had received at least one dose of COVID-19 vaccine before the COVID-19 diagnosis were classified as vaccinated. Data on pregnancy complications, maternal treatment, pregnancy outcomes, and neonatal outcomes, including gestational age at delivery, mode of delivery, and neonatal birthweight, were collected. The composite of pregnancy complications included gestational diabetes mellitus, gestational hypertension and preeclampsia. Patients who required ICU admission or had pneumonia or oxygen requirement were classified as severe COVID-19 cases. Birthweight of less than 2500 g was defined as low birthweight. Neonates born before 37 weeks of gestation were classified as preterm birth. Birthweight percentiles were calculated and adjusted for maternal weight and height, past obstetric history and newborn gender.[15] Fetal growth restriction (FGR) and small for gestational age (SGA) were defined as a birthweight of less than 3rd and 10th percentile for gestational age respectively.

Statistical analysis

Most pregnant women became aware of fetal movements by 20 weeks of gestation,[16] so COVID-19 cases diagnosed before then were excluded in the analysis for this specific clinical presentation. Nonparametric continuous variables were presented as medians with interquartile ranges (IQRs) and analyzed using the Mann-Whitney *U* test. Categorical variables were presented as frequencies and percentages and analyzed using the Pearson's chi-squared test. For analysis with a smaller sample size, the Fisher exact test was used. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 26 (SPSS, IL).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institution, and written consent was obtained before the study. The study was conducted in accordance with the *Declaration of Helsinki*, and the protocol was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (ref CREC 2020.210).

Results

In total, 164 pregnant women with a diagnosis of COVID-19 were recruited and 78 (47.56%) were nulliparous. The number of cases recruited over the study period was illustrated in Figure 1. This cohort represents 163 singleton and 1 twin pregnancies. The median maternal age, weight, and height were 32.00 years (IQR: 29.00–35.00), 56.80 kg (IQR: 51.95–65.23), and 160.00 cm (IQR: 155.00–163.00), respectively. Thirty (18.29%) women were diagnosed with COVID-19 before 28 weeks's gestation and the remaining 134 (81.71%) women were

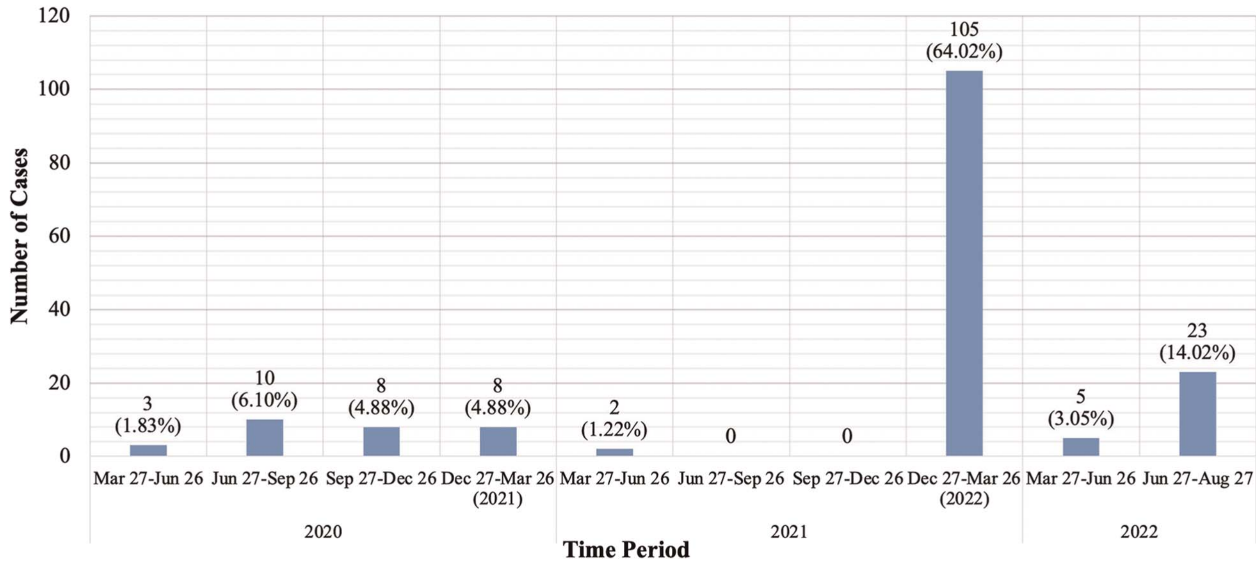

Figure 1. Coronavirus disease case numbers between March 27, 2020, and August 27, 2022 (n = 164).

diagnosed at or after 28 weeks' gestation. Sixty-two (37.80%) of them had been vaccinated with at least one dose of COVID-19 vaccine by the time of the COVID-19 diagnosis.

The median gestational age at COVID-19 diagnosis and delivery was 36.14 weeks (IQR: 31.07–38.29) and 38.71 weeks (IQR: 38.00–39.71) respectively. The median time interval between the diagnosis of COVID-19 and the delivery of the baby was 15.00 days (IQR: 1.00–57.00) and the median Ct value at diagnosis was 24.30 (IQR: 19.58–28.38). The majority of patients, 133 (81.10%), were symptomatic at the time of diagnosis. Cough, sore throat, and fever (53.05%, 47.56%, and 39.63% respectively) were the most common symptoms. Ageusia, anosmia, and diarrhea were the least common symptoms (Table 1). The median birthweight percentile was 52.18th (IQR: 23.82–75.92). Among the 37 patients (22.56%), who experienced decreased fetal movements, four infants were delivered preterm (gestation 34^{+2}–36^{+6} weeks) and two were low birthweight infants (1945–2320 g). None of the pregnancies resulted in an intrauterine death. No statistically significant differences were observed in the gestational age at COVID-19 diagnosis (36.29 weeks *vs*. 36.14 weeks P = 0.935) and delivery (38.64 weeks *vs*. 38.85 weeks, P = 0.261) between the vaccinated and unvaccinated groups. There were no statistically significant differences in the symptoms experienced between the vaccinated and unvaccinated groups except for cough (62.90% *vs*. 47.06%, P = 0.049). In total, 5 (3.05%) patients were classified as having severe COVID-19 in which four of them had oxygen requirements and two were admitted to ICU. Among the severe cases, three were given a combination of steroids, Remdesivir, and antibiotics, one was given steroids and Remdesivir, and the remaining one was only given antibiotics as part of the treatment. Eighty-five (51.83%) women received treatments in the form of oxygen, ICU admission, Remdesivir, steroids, antibiotics, and/or low molecular weight heparin (LMWH). LMWH was the most common treatment given (50.00%). No significant differences were observed in the rate of severe COVID-19 or in the administration of each individual treatment between the vaccinated and unvaccinated groups except for LMWH. Vaccinated patients were more likely to receive LMWH as part of the treatment (62.90% *vs*. 42.16%, P = 0.010).

In terms of pregnancy complications, 17 (10.37%), 7 (4.27%), and 5 (3.05%) cases were complicated with gestational diabetes, gestational hypertension, and preeclampsia, respectively. More pregnancies were complicated by a combination of these conditions in the unvaccinated group than the vaccinated group, however, the difference did not reach statistical significance (18.63% *vs*. 9.68%, P = 0.122). Ninety-nine (60.37%) women had a vaginal delivery; 92 of those had a spontaneous vaginal delivery and seven had an instrumental delivery. Sixty-five (39.63%) patients delivered by cesarean section and 44 of them occurred in an emergency setting. The indications of cesarean sections are summarized in Table 2. No statistically significant difference was demonstrated in the indications of cesarean section between the vaccinated and unvaccinated groups (Table 2, P > 0.05). For fetal outcomes, 14 (8.48%) babies were born preterm; 8, 1, and 5 of them were delivered by emergency cesarean sections, vacuum extraction, and normal vaginal deliveries, respectively. There were nine iatrogenic preterm deliveries, and five and four of them were delivered for maternal and fetal reasons, respectively. Maternal reasons include persistent high fever (n = 2), maternal desaturation (n = 1), antepartum hemorrhage (n = 1), and a diagnosis of preeclampsia with severe features (n = 2). The examples of fetal reasons include suboptimal cardiotocography (n = 2), fetal growth restriction (n = 1), preterm prelabor rupture of membrane (n = 1), and oligohydramnios (n = 1). The iatrogenic preterm deliveries might be indicated for more than one reason. The rest of the preterm deliveries had spontaneous onset. There were four babies (2.65%, n = 151, excluding preterm babies) born with a low birthweight. The percentage of SGA (14.29% *vs*. 13.73%, P = 0.920) and FGR (3.17% *vs*. 4.90%, P = 0.709) babies were similar between the vaccinated and unvaccinated groups. A higher birthweight percentile was observed

Table 1

Clinical summaries of pregnancy outcomes of COVID-19 patients.

Clinical characteristics	Overall (*N* = 164)	Unvaccinated group (0 dose) (*n* = 102)	Vaccinated group (≥1 dose) (*n* = 62)	Statistical value	*P*
Maternal age (year), median (IQR)	32.00 (29.00–35.00)	32.50 (29.00–35.00)	32.0 (27.75–36.00)	3115.50*	0.874
Maternal weight (kg), median (IQR)	56.80 (51.95–65.23)	57.00 (52.00–65.48)	56.10 (50.98–65.48)	2837.00*	0.270
Maternal height (cm), median (IQR)	160.00 (155.00–163.00)	160.00 (155.00–164.00)	159.00 (155.00–162.00)	2953.30*	0.479
Maternal BMI (kg/m^2), median (IQR)	22.25 (20.66–25.16)	23.35 (20.97–25.45)	22.19 (19.84–24.79)	2943.50*	0.459
Gestational age at diagnosis (week), median (IQR)	36.14 (31.07–38.29)	36.14 (30.14–38.46)	36.29 (32.64–37.89)	3138.00*	0.935
<28 weeks, *n* (%)	30 (18.29)	21 (20.59)	9 (14.52)	0.95†	0.329
≥28 weeks, *n* (%)	134 (81.71)	81 (79.41)	53 (85.48)		
Gestational age at delivery (week), median (IQR)	38.71 (38.00–39.71)	38.85 (38.10–39.86)	38.64 (38.00–39.71)	2831.00*	0.261
Interval between diagnosis and delivery (day), median (IQR)	15.00 (1.00–57.00)	15.50 (1.00–65.25)	15.00 (2.75–48.50)	3122.50*	0.893
Ct value at diagnosis, median (IQR)	24.30 (19.58–28.38)	24.35 (19.74–29.60)	24.25 (17.90–27.43)	2817.00*	0.242
Symptomatic of COVID-19, *n* (%)					
Total of symptomatic of COVID-19§	133 (81.10)	78 (76.47)	55 (88.71)	3.77†	0.052
Fever	65 (39.63)	40 (39.22)	25 (40.32)	0.02†	0.888
Cough	87 (53.05)	48 (47.06)	39 (62.90)	3.89†	0.049
Runny nose	46 (28.05)	25 (24.51)	21 (33.87)	1.67†	0.196
Ageusia	3 (1.83)	3 (2.94)	0 (0)	-	0.290‡
Anosmia	6 (3.66)	6 (5.88)	0 (0)	-	0.084‡
Headache	17 (10.37)	12 (11.76)	5 (8.06)	0.57†	0.451
Myalgia	17 (10.37)	14 (13.73)	3 (4.84)	-	0.111‡
Diarrhea	5 (3.05)	4 (3.92)	1 (1.61)	-	0.651‡
Sore throat	78 (47.56)	43 (42.16)	35 (56.45)	3.16†	0.075
Decreased FM (*n* = 151)‖	37 (24.50)	23 (24.73)	14 (24.14)	0.01†	0.934
Maternal outcomes with severe disease, *n* (%)	5 (3.05)	3 (2.94)	2 (3.23)	-	>0.999‡
Patients who received specific COVID-19 treatment, *n* (%)					
Total of any treatment received	85 (51.83)	46 (45.10)	39 (62.90)	4.90†	0.027
Oxygen requirement	4 (2.44)	2 (1.96)	2 (3.23)	-	0.634‡
ICU admission	2 (1.22)	1 (0.98)	1 (1.61)	-	>0.999‡
Remdesivir	5 (3.05)	4 (3.92)	1 (1.61)	-	0.651‡
Steroids	8 (4.88)	6 (5.88)	2 (3.23)	-	0.711‡
Antibiotics	7 (4.27)	5 (4.90)	2 (3.23)	-	0.711‡
LMWH	82 (50.00)	43 (42.16)	39 (62.90)	6.64†	0.010
Mode of delivery, *n* (%)				4.93†	0.177
Spontaneous vaginal delivery	92 (56.10)	61 (59.80)	31 (50.00)		
Instrumental vaginal delivery	7 (4.27)	2 (1.96)	5 (8.06)		
Emergency CS	44 (26.83)	28 (27.45)	16 (25.81)		
Elective CS	21 (12.80)	11 (10.78)	10 (16.13)		
Pregnancy complications, *n* (%)	25 (15.24)	19 (18.63)	6 (9.68)	2.39†	0.122
GDM	17 (10.37)	13 (12.75)	4 (6.45)	-	0.291‡
Gestational HTN	7 (4.27)	4 (3.92)	3 (4.84)	-	>0.999‡
Preeclampsia	5 (3.05)	5 (4.90)	0 (0)	-	0.158‡
Fetal outcomes¶, *n* (%)					
Preterm (*n* = 165)	14 (8.48)	8 (7.84)	6 (9.52)	0.14†	0.707
SGA (*n* = 165)	23 (13.94)	14 (13.73)	9 (14.29)	0.01†	0.920
FGR (*n* = 165)	7 (4.24)	5 (4.90)	2 (3.17)	-	0.709‡
Low birth weight (*n* = 151)**	4 (2.65)	4 (4.26)	0 (0)	-	0.298‡
Birthweight percentile (*n* = 165), median (IQR)	52.18 (23.82–75.92)	50.26 (22.21–74.48)	58.99 (24.40–77.26)	3022.00*	0.522

*Z value for Mann-Whitney U test.

†Chi-squared value for Pearson's chi-squared test.

‡P value from Fisher exact test.

§Participants were either asymptomatic or symptomatic with one or more relevant symptoms.

‖COVID-19 cases diagnosed before 20 weeks gestation were excluded (unvaccinated group $n = 93$, vaccinated group $n = 58$).

¶This cohort consists of 163 single and one twin pregnancies (unvaccinated group $n = 102$, vaccinated group $n = 63$).

**Cases born preterm (<37 weeks) were excluded (unvaccinated group $n = 94$, vaccinated group $n = 57$).

BMI: Body mass index; COVID-19: Coronavirus disease 2019; Ct: Cycle threshold; CS: Cesarean section; GDM: Gestational diabetes mellitus; FGR: Fetal growth restriction; FM: Fetal movement; HTN: Hypertension; ICU: Intensive care unit; IQR: Interquartile range; LMWH: Low molecular weight heparin; SGA: Small for gestational age.

Table 2

Indications of cesarean sections in COVID-19 patients*.

Items	Emergency CS (n = 44)	Elective CS (n = 21)	Unvaccinated group (0 dose) (n = 102)	Vaccinated group (≥1 dose) (n = 62)	Statistical value	P
Fetal distress/bradycardia/suboptimal CTG, n (%)	8 (18.18)	0 (0)	6 (5.88)	5 (8.06)	0.16†	0.685
Previous CS/myomectomy, n (%)	7 (15.91)	7 (33.33)	7 (6.86)	7 (11.29)	0.74†	0.389
Maternal request (delivered in private), n (%)	0 (0)	9 (42.86)	4 (3.92)	5 (8.06)	-	0.465‡
Maternal sepsis/fever/desaturation/COVID-19, n (%)	7 (15.91)	0 (0)	5 (4.90)	2 (3.23)	-	0.693‡
Failed induction of labor, n (%)	7 (15.91)	0 (0)	7 (6.86)	1 (1.61)	-	0.131‡
Gestation hypertension/preeclampsia, n (%)	7 (15.91)	0 (0)	7 (6.86)	1 (1.61)	-	0.131‡
Breech presentation, n (%)	4 (9.09)	4 (19.05)	5 (4.90)	3 (4.84)	-	>0.999‡
Unfavorable cervix, n (%)	4 (9.09)	0 (0)	3 (2.94)	1 (1.61)	-	0.644‡
Antepartum hemorrhage/placenta previa/placenta abruption, n (%)	3 (6.82)	0 (0)	2 (1.96)	1 (1.61)	-	>0.999‡
Fetal growth restriction, n (%)	3 (6.82)	1 (4.76)	3 (2.94)	1 (1.61)	-	0.644‡
No or slow progress/CPD, n (%)	3 (6.82)	0 (0)	3 (2.94)	2 (3.23)	-	>0.999‡
Decreased fetal movement, n (%)	3 (6.82)	0 (0)	2 (1.96)	2 (3.23)	-	>0.999‡
Spontaneous rupture of membrane, n (%)	2 (4.55)	0 (0)	1 (0.98)	3 (4.84)	-	0.293‡
Failed instrumental, n (%)	2 (4.55)	0 (0)	1 (0.98)	1 (1.61)	-	>0.999‡
Suspected intrauterine infection, n (%)	2 (4.55)	0 (0)	1 (0.98)	1 (1.61)	-	>0.999‡
Twin pregnancy, n (%)	0 (0)	1 (4.76)	0 (0)	1 (1.61)	-	0.400‡
Macrosomia, n (%)	0 (0)	1 (4.76)	1 (0.98)	0 (0)	-	>0.999‡
Congenital abnormality of uterus, n (%)	0 (0)	1 (4.76)	1 (0.98)	0 (0)	-	>0.999‡

*Indications of cesarean section were not mutually exclusive.

†Chi-squared value for Pearson's chi-squared test.

‡P value from Fisher exact test.

COVID-19: Coronavirus disease 2019; CS: Cesarean section; CPD: Cephalopelvic disproportion; CTG: Cardiotocography.

in the vaccinated group but the difference did not reach statistical significance (58.99th *vs.* 50.26th, P = 0.522). Overall, no statistically significant differences were observed in pregnancy complications and fetal outcomes between vaccinated and unvaccinated groups.

Discussion

Our study has demonstrated that receiving at least one dose of COVID-19 vaccine does not affect the time interval between diagnosis and delivery, the Ct value, the occurrence of most COVID-19 symptoms at diagnosis, or the mode of delivery in pregnant women who contracted SARS-CoV-2 during their pregnancies. Furthermore, there was also no statistically significant difference in pregnancy complications and fetal outcomes, including the rate of preterm birth and low birth weight, between vaccinated and unvaccinated pregnant women.

In comparison to other countries, the rate of severe COVID-19 disease observed in pregnant patients in our study was very low (3.05%). For instance, a prospective observational cohort study conducted using the United Kingdom Obstetric Surveillance System, across 194 hospitals in the UK reported a rate of severe COVID-19 as high as 20.9% (n = 4436).[17] This rate may have been even higher if our definition of severe disease has been used, as those requiring noninvasive respiratory support were only considered to have moderate disease in their study. In contrast, every patient, who had oxygen requirement, regardless of the mode of respiratory support, was categorized as having severe disease in our study. The low rate of severe COVID-19 observed in pregnant women in Hong Kong is likely due to the city's high vigilance in disease transmission in this well-populated city, including good compliance to universal masking and strict hand hygiene. It has been hypothesized that facemasks can reduce the dosage of viral inoculum, thus reducing the severity of the disease.[18,19] In fact, an observational study on masking behavior carried out in Hong Kong demonstrated that the coverage of facemask usage was already up to 94.8%, among which 83.7% wore disposable surgical masks, in the very beginning of the epidemic in February 2020.[20] The adherence to universal masking could only have further improved as the epidemic progressed as the citizens became more informed about the benefits of facemasks through active promotion from government officials and social media.

Additionally, the disease-attenuating effect of facemasks may be attributed to the increased humidity of inspired air, which promotes mucociliary clearance of pathogens from the lungs.[21] Effective mucociliary clearance can delay and reduce infection of the lower respiratory tract, thereby mitigating disease severity.[21] Hong Kong successfully controlled the SARS-CoV-2 transmission throughout the epidemic by implementing various strategies in addition to universal masking, such as social distancing, widespread testing of symptomatic or high-risk groups for SARS-CoV-2 infections, and strict quarantine measures for close contacts of confirmed COVID-19 cases. The success of these measures is reflected in the relatively small sample size obtained over almost 2.5 years. It was noteworthy that some pregnant women chose to isolate themselves at home throughout their pregnancies during the epidemic to reduce their risk of infection.

The global cesarean section rate has been steadily rising, and Hong Kong is no exception to this trend.[22] A study examining cesarean section rates from 1995 to 2014 in an obstetric unit in Hong Kong observed an increased from 15.4% to 24.6%.[23] In our study, conducted at the local tertiary teaching hospitals where the majority of participants were recruited, an even higher rate of cesarean section (39.63% *vs.* 25.20%) was reported compared to the average rate reported between 2019 and 2021 in the general population. On the other hand, our study showed that the rates of instrumental delivery (4.27% *vs.* 6.73%) and normal vaginal delivery (56.10% *vs.* 68.07%) dropped among COVID-19 patients. These findings are consistent with a previous UK cohort study that also reported an increased cesarean section rate among COVID-19 patients, especially in emergency cesarean section.[7]

One contributing factor to the increased cesarean section rate could be the challenge of ruling out intrauterine infection in laboring COVID-19 patients with fever. In such cases, cesarean sections were often performed to expedite delivery, unless the women were in advanced stages of labor. Furthermore, COVID-19 patients might deliver in isolated facilities, where fetal monitoring could be more difficult. These facilities were also potentially less equipped for instrumental delivery, leading to longer preparation times. These challenges likely influenced healthcare workers to opt for emergency cesarean sections more readily. It is important to note that a more robust study on the impact of COVID-19 on delivery mode would involve a direct comparison between pregnant women, with and without SARS-CoV-2 infection during the same timeframe. This comparison could be considered for future studies using local data.

An overview of systematic reviews on maternal and perinatal outcomes related to COVID-19 published in 2021 highlighted significant variability in the reported rate of preterm delivery among COVID-19 patients.[24] In our study, we observed a slightly higher preterm rate compared to previously published rates of preterm birth in singleton deliveries between 1995 and 2011,[25] as well as the background rate observed between 2020 and 2021 in the same obstetric unit (8.48% *vs.* 6.50% *vs.* 7.90%). The increased rate of cesarean section in our study suggests a higher rate of iatrogenic preterm deliveries, likely contributing to the overall higher preterm birth rate. Moreover, a UK cohort study demonstrated that while COVID-19 did not affect the overall rate of preterm birth, symptomatic COVID-19 patients had a higher rate of preterm birth compared to asymptomatic and uninfected cases.[7] The authors suggested that these findings may indicate early delivery to manage maternal COVID-19 or that symptomatic COVID-19 could lower the threshold for clinicians to intervene for other reasons.[7]

Several studies have demonstrated that COVID-19 vaccination effectively reduces the risk of severe COVID-19 in pregnant patients.[10,26] However, our study did not observe any difference between vaccinated and unvaccinated groups (3.23% *vs.* 2.94%, $P > 0.999$). Subanalysis also indicated that the number of COVID-19 vaccine doses did not significantly affect outcomes, likely due to the low overall incidence of COVID-19 in pregnant women in Hong Kong. Previous research suggested that COVID-19 vaccination was associated with fewer stillbirths but its effect on preterm births was inconclusive.[10] A Melbourne, Australia cohort study provided additional evidence that COVID-19 vaccination was associated with a significant reduction in total preterm births ($P < 0.001$), spontaneous preterm birth ($P = 0.02$) and iatrogenic preterm birth ($P < 0.001$). The decrease in iatrogenic preterm birth might be attributed to less severe COVID-19 presentations postvaccination, resulting in fewer pregnancy interventions. The reduction in spontaneous preterm birth may be related to a dampened systemic inflammation caused by COVID-19 or other nonspecific immune effects.

Our study did not replicate the beneficial effect of COVID-19 vaccination on the rate of preterm birth. In fact, a higher rate of preterm birth was observed in the vaccinated group although this result did not reach statistical significance (9.52% *vs.* 7.84%, $P = 0.707$). We believe this discrepancy is due to the temporal changes of disease severity and incidence of COVID-19 over time. During the evolution of the COVID-19 pandemic, mutations of SARS-CoV-2 generated many variants, impacting their transmissibility, disease characteristic, and their associated morbidity and mortality.[27] Within the first 1000 days of the outbreak, there were five waves of COVID-19 with a total of 1,745,505 cases recorded in Hong Kong.[14] Hong Kong was particularly hit by the fifth wave (primary Omicron wave) between December 2021 and May 2022, in which the incidence of COVID-19 during this period of time was 95 times higher than the total incidence from the first to the fourth wave.[14] A secondary wave of Omicron cases occurred when the BA.5 sublineage emerged in June 2022, becoming the predominant virus strain by August 2022.[14]

Our study demonstrated that COVID-19 had minimal impact on maternal and fetal outcomes, except for significantly higher rate of cough symptoms and prophylactic LMWH treatment among vaccinated pregnant women. Most of our study subjects (81.10%) were diagnosed between December 2021 and August 2022. As the pandemic progressed globally, more was learned about the disease, and international guidelines provided more treatment recommendations. Additionally, more individuals, including pregnant women, received at least one dose of the COVID-19 vaccine at the later stage of the epidemic. The higher rate of LMWH treatment in the vaccinated group was likely multifactorial, including a higher incidence of COVID-19 and an overall higher rate of COVID-19 vaccine uptake. Moreover, there was more evidence supporting the use of prophylactic LMWH as part of COVID-19 managements at the later stage of the pandemic.[28] The spectrum of symptoms during certain periods was also likely affected by the predominated strains of SARS-CoV-2 at that time.

Clinical implications

While our study did not demonstrate the effectiveness of COVID-19 vaccination in reducing maternal and fetal complications, it is important to note that this should not discourage pregnant women from getting the COVID-19 vaccine. Vaccination remains the most effective for preventing severe SARS-CoV-2 infection and building community immunity without contracting the virus. A prospective cohort study[29] in Scotland, UK, involving 131,751 women found that 77.4% of SARS-CoV-2 infections in pregnancy occurred in women who were unvaccinated at the time of onset of disease, with 11.5% and 11.1% in women who received one and two COVID-19 vaccines respectively. Of the infection occurred in unvaccinated women, 19.5% were associated with hospital admission, compared to 8.3% and 5.1% in those with one and two COVID-19 vaccines respectively.

As the world transitions away from strict social distancing and quarantine measures, and Hong Kong has reopened to international travelers, it is important to remain vigilant as future significant waves of COVID-19 are still possible. The XBB variant and its descendant lineages are currently the most prevalent variant in the city. The first shipment of the XBB mRNA vaccine (Comirnaty Omicron XBB.1.5, Pfizer, USA/BioNTech, Germany) arrived in Hong Kong on 30th November 2023. While specific safety data regarding this new bivalent vaccine in pregnancy is unavailable, the extensive information from pregnant women vaccinated with the initially approved Comirnaty vaccine should instill confidence in the new vaccine. When the vaccination program of the new XBB mRNA vaccine becomes available, we advise all pregnant women, who have not received the COVID-19 vaccines, to be vaccinated. Further research is necessary to study the efficacy and timing of booster doses in the long term.

Limitations and strengths

Our study serves as the first report on the maternal and fetal outcomes of COVID-19 cases in Hong Kong. A major strength of the study was its prospective longitudinal design, allowing for near-real-time data collection through a comprehensive medical system with no missing data.

However, our study has several limitations. Firstly, we did not account for the temporal changes in disease severity and evolving knowledge about COVID-19 over time. Secondly, the sample size was limited which made it challenging to adjust for time-dependent exposure, such as infections and vaccinations occurring at different gestational ages.[30] The fact that the study population was recruited by convenient sampling also potentially introduced selection bias. Nevertheless, there was no particular difference in the characteristics between the study subjects and those who were not recruited, and we attempted to minimize the potential bias by recruiting the study population from five waves of COVID-19 epidermic over a reasonable period of time. In the context of COVID-19 epidemic, convenient samplings serve as an efficient way to recruit cases prospectively and allow infectious risks to frontline staffs to be minimized during the sampling process.

Furthermore, we did not consider the time interval between COVID-19 vaccination and diagnosis, which could impact the results as the vaccine's effectiveness may wane over time. This oversight could also mask differences between vaccinated and unvaccinated groups, particularly regarding the risk of very preterm birth. Additionally, the time interval between COVID-19 diagnosis and delivery might also affect the impact of infection on maternal and fetal outcomes, but our analysis was limited by the small sample size.

There is evidence demonstrating that the strain of SARS-CoV-2 contracted is an independent factor affecting the severity of COVID-19, in which the Delta variant is associated with more severe diseases.[31] Our study was limited by not comparing cases caused by different viral strains, despite evidence suggesting strain variation, particularly the Delta variant, can affect disease severity. To address these limitations, we have contributed our data to a bigger meta-analysis looking at risks of adverse maternal and fetal outcomes associated with COVID-19 variants of concern.[32]

Conclusion

Pregnant women with COVID-19 who received at least one vaccine dose showed clinical characteristics similar to those without vaccination. In Hong Kong, the overall rate of severe COVID-19 was low. No significant difference in maternal outcomes was found between vaccinated and unvaccinated groups. Fetal outcomes and pregnancy complications were unaffected by COVID-19 vaccinations, likely due to the small sample size and low COVID-19 incidence in pregnant women in Hong Kong. Despite these findings, COVID-19 vaccination remains highly effective in preventing severe SARS-CoV-2 infections in pregnancy women. While we have adapted to living with the virus and have lifted social distancing measures, ongoing research is crucial to guide management during future waves of COVID-19 and other pandemics.

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Author Contributions

Concept or design: HHY Leung, LC Poon; Acquisition of data: HHY Leung, S Moungmaithong, TWL Ma, FN Yu, MCW Kong, TK Lo, PPL So, WC Leung, W Shu, KW Cheung; Analysis or interpretation of data: HHY Leung, LC Poon; Drafting of the manuscript: HHY Leung, LC Poon; Critical revision of the manuscript for important intellectual content: HHY Leung, LC Poon, CC Wang, KW Cheung, PPL So. 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

None.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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