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Pregnancy Outcomes among Singleton Pregnant Women with Coronavirus Disease 2019 Infection: A single-center study in Thailand

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ABSTRACT

Objectives: We aimed to describe the outcomes between singleton pregnant women with and without coronavirus disease 2019 (COVID-19) infection.

Materials and Methods: A retrospective study of pregnancy outcomes was conducted among pregnant women delivered in Khon Kaen Hospital with universal nasopharyngeal swab realtime reverse transcription polymerase chain reaction (RT-PCR) tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between August 1, 2021, and August 31, 2022. A total of 230 pregnant women were included in this study: the COVID-19-positive group (n = 115) and the COVID-19-negative group (n = 115). Adverse pregnancy outcomes were determined, including preterm delivery, preeclampsia, cesarean delivery, placental abruption, clinical chorioamnionitis, stillbirth, intensive care unit (ICU) admission, and maternal length of stay. In addition, neonatal outcomes recorded included birth weight, meconium-stained amniotic fluid, 5-min Apgar score, neonatal intensive care unit (NICU) admission, mechanical ventilation used in the first 24 h, required continuous positive airway pressure (CPAP) in the first 24 h, neonatal sepsis and a result of neonatal SARS-CoV-2 RT-PCR tested.

Results: Preterm delivery was significantly greater among the COVID-19-infected women (35.6%) than among the non-COVID-19-infected women (27.8%) (odds ratio 6.36, 95% confidence interval (CI) 1.71-8.15, p = 0.026). The length of hospital stay was also significantly longer in the COVID-19-infected group (7.89 ± 3.26 vs 2.82 ± 0.79 days, odds ratio 11.46, 95%CI 3.85-34.12, p < 0.001). Most pregnant women with COVID-19 infection had mild symptoms (36.5%). Two (1.7%) had severe pneumonia and required mechanical ventilation. No significant differences in neonatal outcomes and no vertical transmission were detected in this study.

Conclusion: Pregnant women with COVID-19 infection were at significantly increased risk of preterm delivery and had a longer hospital stay.

Keywords: coronavirus disease 2019, pregnancy outcomes, preterm delivery, COVID-19.

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ผลลัพธ์การตั้งครรภ์ในสตรีตั้งครรภ์เดี่ยวที่ติดเชื้อไวรัสโคโรนา 2019 : การศึกษาในสถาบันเดียว

วศวัตติ์ พัฒนะชัยรุจน์, ธัญธร ศรีสถาพร, อุษณีย์ สังคมกำาแหง, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาผลลัพธ์การตั้งครรภ์ในสตรีตั้งครรภ์ที่ติดเชื้อโควิด-19 เปรียบเทียบกับสตรีตั้งครรภ์ที่ไม่ติดเชื้อ***วัสดุและวิธีการ****: การศึกษาแบบ Retrospective study ระหว่างวันที่ 1 สิงหาคม 2564-31 สิงหาคม 2565 ในสตรีตั้งครรภ์ที่มาคลอดบุตร ณ โรงพยาบาลขอนแก่นและได้รับการตรวจหาเชื้อไวรัสโคโรนา 2019 จากเยื่อโพรงจมูกและคอหอยด้วยวิธี RT-PCR (Real time reverse transcription polymerase chain reaction) ทำการเก็บข้อมูลจากสตรีตั้งครรภ์ที่ติดเชื้อโคโรนาไวรัส 2019 จำนวน 115 คน เปรียบเทียบกับกลุ่มที่ไม่ติดเชื้อจำนวน 115 คน ข้อมูลที่ศึกษา ได้แก่ ข้อมูลพื้นฐานของมารดา ผลลัพธ์ของการตั้งครรภ์และการคลอด ภาวะแทรกซ้อน และผลลัพธ์ในทารกแรกเกิด*

ผลการศึกษา: *สตรีตั้งครรภ์ที่ติดเชื้อไวรัสโคโรนา 2019 มีอัตราการคลอดก่อนกำหนดสูงกว่าสตรีตั้งครรภ์ที่ไม่ติดเชื้อ (ร้อยละ 35.65 และร้อยละ 27.83 ตามลำดับ, อัตราส่วนออด 6.36, ช่วงความเชื่อมั่นร้อยละ 95 1.71-8.15) และมีระยะเวลาการนอนโรงพยาบาลที่ยาวนานกว่า (7.89 ± 3.26 วัน และ 2.82 ± 0.79 วัน ตามลำดับ, อัตราส่วนออด 11.46, ช่วงความเชื่อมั่นร้อยละ 95 3.85-34.12) สตรีตั้งครรภ์ที่ติดเชื้อส่วนใหญ่ (ร้อยละ 36.52) มีอาการไม่รุนแรง แต่พบสตรีตั้งครรภ์ 2 ราย (ร้อยละ 1.74) มีอาการปอดติดเชื้อรุนแรง ต้องใช้เครื่องช่วยหายใจและเข้ารับการรักษาตัวในหอผู้ป่วยหนัก ทั้งนี้ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญในผลลัพธ์ของทารกแรกเกิด และไม่พบว่ามีการถ่ายทอดเชื้อไวรัสโคโรนา 2019 จากมารดาสู่ทารก*

สรุป*: สตรีตั้งครรภ์ที่ติดเชื้อไวรัสโคโรนา 2019 เพิ่มอัตราการคลอดก่อนกำหนดและมีระยะเวลาในการนอนโรงพยาบาลนานกว่าสตรีตั้งครรภ์ที่ไม่ติดเชื้ออย่างมีนัยสำคัญ*

คำสำคัญ*: โคโรนาไวรัส 2019, ผลลัพธ์การตั้งครรภ์, สตรีตั้งครรภ์, การคลอดก่อนกำหนด, โควิด-19*

Introduction

The COVID-19 pandemic has spread worldwide since the first case in Wuhan City (Hubei Province, China) in December 2019. By 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected more than 182 million people globally, with more than 3.9 million deaths[1].

Thailand was the first country to report a case outside China. On January 13, 2020, the Ministry of Public health reported the first confirmed COVID-19 case in a Wuhan resident who traveled to Bangkok. Subsequently, the first locally transmitted cases were reported on January 31, and cases continued to increase, and the epidemic was widespread. As of April 2022, the country had reported a cumulative total of 3,684,755 confirmed cases, with 25,318 deaths from the disease[2].

SARS-CoV-2 is an enveloped, positive-stranded RNA beta-coronavirus, the International Committee on Taxonomy of Viruses Study Group proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus infects host respiratory epithelial cells through the angiotensin-converting enzyme-2 (ACE2) receptor, predominantly within type II alveolar lung cells. Extrapulmonary sites also occur in the heart, blood vessels, kidneys, liver, and gastrointestinal tract.

The estimated incubation period is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days[3]. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. The mortality rate is higher in those older than 70 years, regardless of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular diseases, 30% had diabetes, and 18% had chronic lung diseases. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney diseases, obesity, and other immunocompromising conditions. Pregnant women are also at increased risk for severe illness associated with COVID-19[4] due to their susceptibility to respiratory pathogens such as decreased lung capacity, immunologic changes, and increased risk for thromboembolic diseases. Furthermore, the pregnancy bias toward T-helper 2 (Th2) system dominance protects the fetus but leaves the mother vulnerable to viral infections, more effectively contained by the Th1 system.

The association between COVID-19 and adverse pregnancy outcomes was unclear. Some evidence indicated that an unfavorable cluster of differentiation 4 (CD4) cell phenotype raised concerns about disordered implantation and placentation[5] and the possibility of developing fetal growth restriction, preeclampsia, and other consequences of placental dysfunction. COVID-19 is also associated with a profound prothrombotic state, particularly with the formation of immunogenic thrombi in the microvasculature[6], and there is also an increased risk of poor obstetric outcomes among pregnant women[7]. Symptomatic maternal COVID-19 is associated with an increased likelihood of preterm birth. It may also be associated with an increased incidence of small for gestational age babies[8], and it seems likely that neonatal morbidity for babies born to mothers with COVID-19 infection is linked to preterm birth, while stillbirth remains a rare outcome.

Many studies showed the adverse effects of COVID-19 infection to pregnancy outcomes, but some data are still controversy[9]. We thus aimed to compare pregnancy outcomes among pregnant patients with and without COVID-19 infection at the delivery time.

Materials and Methods

This was a case-control study of pregnancy outcomes among pregnant patients who delivered

at Khon Kaen Hospital between August 1, 2021 to August 31, 2022. The research protocol was approved by the Khon Kaen Hospital Institute Review Board in Human Research (KEXP65052).

The sample size was calculated using the formula for case-control studies and based on previous data[10]. The estimated rate of preterm birth in COVID-19 pregnant women was 0.22, and the rate of preterm birth in pregnant women without COVID-19 was 0.08 with an acceptable error (alpha) of 0.05, beta of 0.20, Z1-$\propto$/2 of 1.96 and Z1-β of 0.80. The continuity correction sample size thus included 230 cases, 115 pregnant women with COVID-19 and 115 pregnant women without COVID-19. The authors selected the ratio (case: control) of 1:1 based on maternal age, gestational age at delivery, and delivery date.

Pregnant women admitted to the labor room or delivery units during the study period were included, and universal SARS-CoV-2 RT-PCR testing was performed. Diagnosis of COVID-19 infection was made by real-time reverse transcription polymerase chain reaction (RT-PCR) detected SARS-CoV-2 nucleic acid from nasopharyngeal specimens. Eligible patients were then divided into two groups, a positive-COVID-19 group, and a negative-COVID-19 group. Pregnancy with multifetal gestations was excluded from this study. In addition, hospital admission logs were reviewed to ensure complete data capture of all delivered women.

Baseline characteristics were recorded, including maternal age, body mass index (BMI), parity, comorbidities, and doses of COVID-19 vaccination. Among women with COVID-19 infection, our study classified maternal disease severity at presentation according to the National Institutes of Health (NIH) COVID-19 illness severity classification[11], including asymptomatic, mild, moderate, severe, and critical illness. Asymptomatic or presymptomatic infection was defined as individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but with no symptoms consistent with COVID-19. Mild illness was defined as individuals with any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but with no shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness was defined as individuals showing evidence of lower respiratory disease during clinical assessment or imaging and with oxygen saturation (SpO2) ≥ 94% on room air at sea level. Severe illness was defined as individuals with a SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates > 50% and critical illness was defined as individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Treatment of COVID-19 during pregnancy depended on the severity of the illness. In our hospital treatment policy, COVID-19-infected women were admitted to the obstetrics cohort ward with standard intrapartum care and delivered by an obstetrician staff or resident doctor with a multidisciplinary team. We classified pregnant women according to the NIH illness severity scale. In mild and moderate illnesses, symptomatic treatment was given, including hydration, antipyretics, analgesics, and antitussives. Medical consultation with internal medicine and infectious disease staff was obtained in severe and critical illness cases. Those patients who required mechanical ventilation were admitted to the intensive care unit (ICU), and therapeutic management included respiratory support, antiviral drugs, and corticosteroids.

Preterm labor was treated with the same protocol in both groups. Pregnant women

admitted with preterm labor underwent universal RT-PCR testing for SARS-CoV-2. Women infected with COVID-19 were moved to an isolation room and treated with tocolytic agents. Per our hospital guidelines, Nifedipine was the first line drug, and terbutaline (Bricanyl) was the second choice when nifedipine was failed unless contraindicated (i.e., in cardiac disease, maternal tachycardia, or poorly controlled diabetes mellitus (DM). Magnesium sulfate was given for neuroprotection in case of preterm labor at gestational age less than 32 weeks. A dexamethasone dose of 6 mg intramuscular injection (IM) was given every 12 h: 4 doses were given in case of preterm labor with a gestational age of fewer than 34 weeks with a high risk for preterm delivery in the next 7 days.

The primary outcome was preterm delivery (delivery before 37 weeks gestation, including spontaneous and indicated preterm delivery) and the secondary outcomes were cesarean delivery, placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, mechanical ventilation, length of stay and the neonatal outcomes including birth weight, meconium-stained amniotic fluid, 5-min Apgar score, Neonatal Intensive Care Unit (NICU) admission, mechanical ventilation used in the first 24 h, required continuous positive airway pressure (CPAP) in the first 24 h, neonatal sepsis, and results of neonatal SARS-CoV-2 RT-PCR tests.

Statistical analyses were done using STATA 16 computer software. Baseline characteristics were analyzed using chi-square or Fisher's exact test and presented as numbers and percentages. Continuous data were analyzed using the student's t-test and presented as means with standard deviation (SD). Pregnancy outcomes were compared between women with and without SARS-CoV-2 infection. Logistic regression analyses were performed using the t-test for continuous outcomes and the Pearson $\chi 2$ test for categorical outcomes. The p values for all hypotheses were 2-sided, and the statistical significance was set at $p < 0.05$. Effect sizes were presented as odds ratio (OR) with 95% confidence intervals (CIs).

Results

Two hundred and thirty pregnant women were included between August 1, 2021, and August 31, 2022, comprising a COVID-19 positive group (n = 115) and a COVID-19 negative group (n = 115). The baseline characteristics of the participants are shown in Table 1. The mean age of pregnant women with a COVID-19 infection was 27.7 ± 5.7 years, most of whom were multiparous (73.91%). The median gestational age at delivery was 37 1/7 weeks (interquartile range (IQR) 321/7 to 406/7) in COVID-19 positive group and 37 3/7 (IQR 32 to 41) weeks in COVID-19 negative group (p = 0.92). The two groups had no significant differences in maternal age, BMI, parity, or co-morbidities but in the number of COVID-19 vaccination doses (p = 0.020). Pregnant women who got COVID-19 infection had never get vaccination in higher percentage (19.13% vs 14.78%) compared with those who did not get infection. However, 40% of those who got COVID-19 infection had received two or more vaccination doses. Women who received 2 or more vaccine doses were less common in the COVID-19-positive group (40.0% vs 58.3%) than in the COVID-19-negative group. Among pregnant women with COVID-19 infection, 36.5% had a mild illness, 33.0% had no symptoms, 26.1% had moderate illness, 2.6% had severe illness, and 1.7% had critical illness. In cases of severe and critical illness, there were three pregnant patients with COVID-19 pneumonia that required mechanical ventilation and two patients had septic shock with respiratory and kidney failure.

Table 1. Baseline characteristics.

Characteristic	COVID-19 positive (n = 115)	COVID-19 negative (n = 115)	p value
Age (years), mean ± SD	27.70 ± 5.66	27.21 ± 5.41	0.498
Gestational age at delivery (weeks), median (IQR)	$37^{1/7}$ ($32^{1/7}$ to $40^{6/7}$)	$37^{3/7}$ (32 to 41)	0.92
BMI (kg/m^2), n (%)			0.758
< 18.5	22 (19.13)	18 (15.65)	
18.5-24.9	18 (15.65)	23 (20.00)	
25-25.9	51 (44.35)	48 (41.76)	
≥ 30	24 (20.87)	26 (22.61)	
Parity, n (%)			0.761
Nulliparous	30 (26.09)	28 (24.35)	
Multiparous	85 (73.91)	87 (75.65)	
Comorbidities, n (%)			0.904
Chronic hypertension	8 (6.96)	10 (8.70)	
Diabetes mellitus	10 (8.70)	12 (10.43)	
Asthma	5 (4.35)	4 (3.48)	
None	92 (80.00)	89 (77.39)	
COVID Vaccination, n (%)			0.020*
None	22 (19.13)	17 (14.78)	
1 dose	47 (40.87)	31 (26.96)	
2 doses or more	46 (40.00)	67 (58.26)	
NIH severity classification, n (%)			NA
Asymptomatic	38 (33.04)		
Mild illness	42 (36.52)		
Moderate illness	30 (26.09)		
Severe illness	3 (2.61)		
Critical illness	2 (1.74)		

BMI: body mass index, NIH: National Institute of Health, SD: standard deviation, IQR: interquartile range, n: number of patients

Pregnancy outcomes are presented in Table 2. In the COVID-19-positive group, term delivery accounted for 64.4% of births, and preterm delivery 35.7%. In the COVID-19-negative group, term delivery accounted for 72.2%, while preterm delivery was lower (27.8%). In the COVID-19-positive group, 56.5% of pregnant women (65/115 cases) were delivered by cesarean section, and emergency cesarean section accounted for 87.7% of cases. In the COVID-19-positive group, the indications for cesarean delivery were previous cesarean delivery (29 cases, 44.6%), cephalopelvic disproportion (22 cases, 33.9%), non-reassuring fetal status (7 cases, 10.8%), abnormal presentation (5 cases, 7.7%) and other 2 cases accompanying severe maternal COVID-19 pneumonia included septic shock to improve maternal hemodynamic stability.

In the COVID-19-positive women, the proportion of cesarean section in the term delivery group was 78.5% (51/65 cases), and the indications were previous cesarean delivery (24 cases, 36.9%), cephalopelvic disproportion (20 cases, 30.8%), non-reassuring fetal status (4 cases, 6.15%) and abnormal presentation (3 cases, 4.6%). Whereas cesarean section in the preterm delivery group was 21.5% (14/6 cases), and the indications were previous cesarean delivery (5 cases, 7.7%), non-reassuring fetal status (3 cases, 4.6%), cephalopelvic disproportion (2 cases, 3.1%), abnormal presentation (2 cases, 3.1%) and others (2 cases, 3.1%).

In addition, the maternal length of stay of women with COVID-19 infection was significantly longer than women without COVID-19 infection (7.89 ± 3.26 vs 2.82 ± 0.79 days, OR 11.46, 95%CI 3.85-34.12, p < 0.001).

Finally, there were no statistically significant differences between the two groups in maternal outcomes

of placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, and mechanical ventilation. In addition, there were no statistically significant differences between groups in infants born to COVID-19-positive mothers. No vertical transmission of COVID-19 was detected in this study.

Table 2. Obstetrics and neonatal outcomes among delivered women with and without SARS-CoV-2 infection.

Outcome	COVID-19 positive (n = 115)	COVID-19 negative (n = 115)	p value	Odds ratio (95% CI)
Term delivery, n (%)	74 (64.35)	83 (72.17)	0.439	-
37 - 38^{+6}	42 (36.52)	55 (47.83)		
39 - 39^{+6}	25 (21.74)	23 (20.00)		
40 or more	7 (6.09)	5 (4.35)		
Preterm delivery, n (%)	41 (35.65)	32 (27.83)	0.026	6.36 (1.71-8.15)
Mode of delivery, n (%)				
Vaginal delivery	50 (43.48)	42 (36.52)	0.508	-
Spontaneous	49 (98.00)	36 (85.71)		
Operative (V/E, F/E)	1 (2.00)	6 (14.29)		
Cesarean delivery	65 (56.52)	73 (63.48)	0.282	-
Elective	8 (12.31)	54 (73.97)		
Emergency	57 (87.69)	19 (26.03)		
Indications for C/S, n (%)				
Non-reassuring fetal status	7 (10.77)	5 (6.85)	0.514	-
Abnormal presentation	5 (7.69)	2 (2.74)	0.274	-
CPD	22 (33.85)	19 (26.03)	0.104	-
Previous cesarean delivery	29 (44.62)	42 (57.53)	0.273	-
Others	2 (3.08)	5 (6.85)		
Placental abruption, n (%)	1 (0.87)	3 (2.61)	0.313	-
Clinical chorioamnionitis, n (%)	1 (0.87)	2 (1.74)	0.561	-
Stillbirth, n (%)	0 (0.00)	2 (1.74)	0.155	-
Gestational hypertension, n (%)	2 (1.74)	4 (3.48)	0.408	-
Preeclampsia, n (%)	8 (6.96)	14 (12.17)	0.808	-
Without severe feature	5 (62.50)	8 (57.14)		
With severe feature	3 (37.50)	6 (42.86)		
ICU admission, n (%)	3 (2.61)	0 (0.00)	0.081	-
Mechanical ventilation used, n (%)	2 (1.74)	0 (0.00)	0.498	-
Maternal length of stay (days); mean ± SD	7.89 ± 3.26	2.82 ± 0.79	< 0.001	11.46 (3.85-34.12)
Neonatal outcomes				
Birthweight (grams); mean ± SD	2920.69 ± 561.60	2876.43 ± 568.97	0.552	-
5-min APGAR score, n (%)				
7 - 10	112 (97.39)	113 (98.26)	0.651	-
< 7	3 (2.61)	2 (1.74)	0.449	-
Meconium-stained amniotic fluid, n (%)	8 (6.96)	15 (13.04)	0.765	-
NICU admission, n (%)	9 (7.83)	12 (10.43)	0.492	-
Mechanical ventilation in first 24 hr, n (%)	4 (3.48)	4 (3.48)	0.229	-
CPAP in first 24 hr, n (%)	13 (11.30)	8 (6.96)	0.547	-
Neonatal sepsis, n (%)	8 (6.96)	10 (8.70)	0.706	-
Neonatal RT-PCR for SARS-CoV-2, n (%)				
Detected	0 (0.00)		NA	
Not detected	115 (100.00)			

SD: standard deviation, n: number of patients, V/E: vacuum extraction, F/E: forceps extraction, C/S: cesarean section, CPD: cephalopelvic disproportion, NA: not applicable, NICU: neonatal intensive care unit, CPAP: continuous positive airway pressure, RT-PCR: real-time reverse transcription polymerase chain reaction

Discussion

Our results showed that the rate of preterm delivery was significantly higher among the COVID-19-positive group, 35.7% (41/115) vs 27.8% (32/115) in the COVID-19-negative group (OR 6.36, 95%CI 1.71-8.15, p= 0.026). Our results agreed with a systematic review by Maryamsadat et al[12], who reported that preterm birth was more likely among pregnant women with COVID-19 than pregnant women without COVID-19. Similarly, Shu et al[13] found that having COVID-19 while pregnant was associated with preterm birth and a higher maternal and neonatal morbidity risk. Allotey et al[14] likewise found that pregnant women with covid-19 were more likely to deliver preterm. Finally, Oralkhan et al[15] performed a systematic review from twenty-six cohort studies and found that COVID-19 was associated with a significantly increased risk of preterm birth, corresponding with a study by Anggraini et al[16] who showed that there was a significant relationship between COVID-19 and increased incidence of preterm birth. Notwithstanding, Adhikari et al[17] performed a large, single-institution cohort study and found no differences in preterm birth composite outcomes. Similarly, Barbara et al[18] reported that preterm births before 37 weeks' gestation were not significantly changed. Similarly, Pirjani et al[19] and Mullin et al[20] found that the prevalence of preterm birth did not differ significantly during the COVID-19 pandemic compared to the pre-pandemic period.

Preterm delivery was influenced by multiple factors, and it is critical to understand the mechanism that explains the link between preterm delivery and SARS-CoV-2 infection and identifies effective prevention methods to avoid COVID-19-caused adverse pregnancy outcomes. Numerous studies have demonstrated that the pathogen may cause exaggerated systemic inflammatory responses, which may interfere with the placenta's optimal condition for fetal growth and development[21] and vascular malperfusion of the placental-fetal unit may be another contributing factor to developing adverse pregnancy outcomes.

According to Thresa et al[22] the COVID-19 pandemic has had a disproportionate impact on the mental health of pregnant women, including stress, worry, and anxiety. As such, mental health disorders are associated with intrauterine growth restriction or preterm delivery due to the activation of the human platelet antigen (HPA) axis by mothers who experience stress during pregnancy. Consequently, the fetus may be stressed by increased concentrations of corticotropin-releasing hormone (CRH) in the fetal plasma, amniotic fluid, and maternal plasma compared to levels in normal pregnancy. In the current study, however, the exact cause of preterm birth in COVID-19-infected pregnant women is unknown. Future research is required to collect additional data to further validate or corroborate these findings, to better comprehend these associations, and to identify effective strategies to prevent adverse outcomes in pregnant women infected with COVID-19.

More than half of COVID-19 pregnant women (65/115 cases, 56.52%) were delivered by cesarean section. Most cases were emergency cesareans (57/65 cases, 87.7%). The indications for cesarean section among COVID-19 pregnant patients were previous cesarean delivery (29 cases, 44.6%), cephalopelvic disproportion (22 cases, 33.9%), non-reassuring fetal status (7 cases, 10, 8%), and abnormal presentation (5 cases, 7.7%). Other conditions accompanying severe maternal COVID-19 pneumonia included septic shock to improve hemodynamic stability. Compared with non-infected women, our study showed that the cesarean section rate was not significantly higher (56.5% vs 63.5%, p = 0.282), unlike Maryamsadat et al[12], Jean et al[23], and Phabhu et al[24], who reported that cesarean delivery occurred more often among pregnant women with COVID-19. Further studies on changing cesarean section trends during the pandemic are needed.

The current study found that the maternal length of hospital stay of women with COVID-19 infection was significantly longer than women without COVID-19 infection (7.89 ± 3.26 vs 2.82 ± 0.79 days, p < 0.001). This might be because during the early pandemic in

Thailand, and accordance with our hospital treatment policy, all infected patients, regardless of symptoms, were required to be hospitalised to ensure they received proper care and prevent the spread of the virus to the community. In contrast, hospital stays for patients with moderate to critical illnesses requiring oxygen therapy, mechanical ventilation, or intensive care, should be longer. However, the latest wave (the omicron wave - the sixth) led to a sharp rise in the number of new COVID-19 cases, and this increase in the number of patients overwhelmed many hospitals. In addition, hospitals had already reached full capacity with asymptomatic patients or those with mild illnesses who did not require oxygen therapy. Home isolation had then become a suitable option for those caring for themselves.

According to our hospital policy during the pandemic, all infants born to COVID-19-positive mothers were isolated, and a nasopharyngeal RT-PCR swab test was performed at 24 and 72 hours postpartum. In our study, no vertical transmission was detected. Although vertical transmission of SARS-CoV-2 is possible, the current data suggest it is rare. Chen et al[25] showed that SARS-CoV-2 was negative in all the amniotic fluid, cord blood, breast milk and neonatal nasopharyngeal swabs. By contrast, few cases of intrauterine SARS-CoV-2 transmission have been documented by the study of Vivanti et al[26] reported a proven case of transplacental transmission of SARS-CoV-2 from a pregnant woman affected by COVID-19 during late pregnancy. In addition, infection in neonates is more likely due to close contact after delivery according to the findings of Martinez-Perez et al[27], PCR analysis was performed on samples of the nasopharynx and oropharynx of 147 newborns during the first 12 and 48 hours of life, 3 of which were positive in the first 12 hours and all three newborns who had an initial positive result were retested at 48 hours, with a final negative result.

There were no significant differences in the baseline characteristics of the two groups vis-à-vis maternal age, BMI, parity, and co-morbidities. However, this study showed that pregnant women who were never vaccinated were more likely to be infected with COVID-19 (19.1% vs 14.8%), while women who received 2 or more doses were less likely (40.0% vs 58.3%). These results provide further evidence that vaccination against COVID-19 is protective for all pregnant women and that the vaccines are safe and effective during pregnancy. In addition, Atsuyuki et al[28] performed a systematic review, and the results showed that vaccination during pregnancy was not associated with an increased the risk of adverse peripartum outcomes, but decreased risk of NICU admission, intrauterine fetal death, and maternal infection. Thus, COVID-19 vaccination should be encouraged for all pregnant. Furthermore, in 2021 Shimabukuro et al[29] reported that the production of IgG antibodies and their subsequent transfer improved after the second dose of either vaccine. Baoqi Zeng et al[30] showed that booster vaccination doses were more effective against Delta and Omicron variants and women who got booster vaccination were less likely to suffered from severe COVID-19 diseases. In addition, according to Phupong[31], prevention is the best way to avoid COVID-19. Regular hand washing, covering the mouth and nose when coughing and sneezing, and avoiding close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing are all standard recommendations for coronavirus infections.

As of March 2022, the country had reported number of pregnant women with COVID-19 infection are more than 7,210 and 110 patients were dead. The reports of disease severity among pregnancy with COVID-19 infection by Torri et al[32] found that most patients with a positive SARS-CoV-2 test were asymptomatic and according to a study by Phupong[31], the clinical characteristics of COVID-19 in pregnant women were the same as those of non-pregnant adults in the general population and Seema et al[33] compared maternal clinical characteristics during first and second waves of COVID-19 in pregnant women in India, the results found that fever and sore throat were common presenting symptoms and most women

with underlying disease such as asthma and cardiac disease progressed to severe or critical illness. In our study, among women with COVID-19 infection, most had mild symptoms (36.5%) (i.e., cough, myalgia, fever, sore throat, or nasal stuffiness), importantly, our findings revealed that 4.4% of all delivered women with SARS-CoV-2 infection developed severe and critical illness, which are lower than rates reported by Andrikopoulou et al[34].

Although our study period included the two different waves of infection (Delta and Omicron), which may have influenced disease severity, a study by Birol et al[35] found that disease severity was comparable between the two waves, and infection in unvaccinated pregnant women carried a considerable risk of morbidity and mortality regardless of variant, in the same way. Seema et al[33] showed that the clinical characteristics and severity of the disease did not differ significantly in the first and second waves of COVID-19. However, Kensuke et al[36] reported the clinical manifestations of COVID-19 in pregnant women differed between the Delta and Omicron periods, and Sarah et al[37] discovered that infection during the Omicron-dominant period (compared with the Delta-dominant period) was associated with significantly lower risk for critical care admission and preterm birth.

The present study showed no differences between the two groups in obstetric complications (viz. placental abruption, clinical chorioamnionitis, stillbirth, gestational hypertension, preeclampsia, ICU admission, and mechanical ventilation). In addition, no statistically significant differences were found among infants born to mothers with COVID-19 infection. This observation may be due to a small sample size that could not detect the difference. In contrast, Fhabian et al[38] investigated maternal and fetal outcomes in pregnant women hospitalized with COVID-19 in Venezuela; the findings revealed that the most common maternal complications were anemia, oligohydramnios, hypertensive disorders of pregnancy, and low birth weight. There was furthermore an increased risk of stillbirth and abortions in pregnant women with COVID-19 infection. Furthermore, studies by Wong[39] and Alfaraj[40] showed that SARS and Middle East respiratory syndrome coronavirus (MERS-CoV) infection were associated with a high incidence of maternal and neonatal complications such as spontaneous abortion, intrauterine growth restriction, and ICU admission. Notwithstanding, in pregnant women with COVID-19 (SARS-CoV-2) has fewer adverse maternal and neonatal complications than those viruses.

The strengths of our study were that it was a matched case-control and a single-center study, despite the limitations of a retrospective design, a small sample size, and a study period that included different clinical manifestations of disease (viz., the Delta and Omicron waves).

Conclusion

Pregnant women with COVID-19 infection were at significantly increased risk of preterm delivery and had a longer hospital stay.

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Potential conflict of interest

The authors declare no conflicts of interest.

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