

Birth Outcomes of Pregnant Women Infected with COVID-19 in Highland Areas of China from 2020 to 2022: A Retrospective Analysis

Aiming Lv^{1,2}, Bian Ba Zhuo Ma³, De Qiong², Da Wa Zhuo Ma², Pu Bu Zhuo Ma³, Donghua Yao⁴, Da Zhen², Chunxiu Tang², Bian Ba Zhuo Ma², Youzhi Lu², Long Cai², Yutong Zhang², Jinyu Yin², Tong Ding², Lang Ji Qu Zhen², Da Wa Cang⁵, Meng Wu⁵, Yulan Chen⁵, Ye Li¹

¹Department of Obstetrics and Gynecology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, People's Republic of China; ²Department of Obstetrics and Gynecology, Women and Children's Hospital of Tibet Autonomous Region, Lhasa City, TB, People's Republic of China; ³Department of Obstetrics and Gynecology, Lhasa People's Hospital, Lhasa, TB, 850000, People's Republic of China; ⁴Department of Obstetrics and Gynecology, Nyingchi People's Hospital, Nyingchi City, TB, People's Republic of China; ⁵Department of Obstetrics and Gynecology, Tibet University Medical School, Lhasa City, TB, People's Republic of China

Correspondence: Ye Li, Department of Obstetrics and Gynecology, Beijing Hospital, National center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, China, No. 1 DaHua Road, Dong Dan, Beijing, 100730, People's Republic of China, Tel +86 13611118475, Fax +86 10 85136220, Email liyewtfy@126.com

Purpose: To explore the effect of coronavirus disease 2019 (COVID-19) infection on neonates in plateau regions.

Methods: Cases of newborns born to pregnant women infected with COVID-19 who received prenatal care or treatment at the Women and Children's Hospital of the Tibet Autonomous Region and the Lhasa People's Hospital between January 2020 and December 2022 (infected group) and newborns born to healthy pregnant women (non-infected group) who were included by age, underlying disease and length of hospital stay were retrospectively collected. According to the inclusion and exclusion criteria, 381 patients in the infected group and 314 patients in the non-infected group were included in the study.

Results: The results of multivariate analysis showed that admission to the neonatal intensive care unit (OR = 3.342, 95% CI = 1.564–6.764), shortness of breath (OR = 2.853, 95% CI = 1.789–3.154), irregular breathing (OR = 2.465, 95% CI = 1.879–4.112) and neonatal jaundice (OR = 2.324, 95% CI = 1.989–2.445) were the factors influencing the low Apgar scores of neonates in the infected group (all $P < 0.05$).

Conclusion: Neonates born to pregnant women infected with COVID-19 had lower Apgar scores and higher incidences of complications, such as shortness of breath, groaning, irregular breathing and neonatal jaundice, than newborns born to pregnant women not infected with COVID-19.

Keywords: COVID-19, pregnant women, newborn

Introduction

The pathogen of coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the group of betacoronaviruses that includes other members, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) that became widespread across the globe with high morbidity and mortality.^{1–3} The SARS-CoV-2 invades cells by binding the spike protein (S protein) with the angiotensin-converting enzyme 2 (ACE2).⁴ The SARS-CoV-2 and the SARS-CoV have a similar affinity to the ACE2, but the former has a high incidence of infection due to its mutability.^{5–7}

The physiological changes in immune, respiratory and circulatory systems during pregnancy make pregnant women susceptible to pathogens and intolerant to hypoxia.^{8–10} Pregnant women have a higher risk of viral infections, complications and adverse clinical and pregnancy outcomes compared with the general population.¹¹ Controversy exists about whether a novel coronavirus infection impacts neonatal outcomes.^{12–16} Some studies have found no

significant increase in the incidence of adverse neonatal outcomes in pregnant women who tested positive for COVID-19 compared with pregnant women who tested negative.^{17,18} Conversely, some studies have shown an increased risk of adverse neonatal outcomes in pregnant women who tested positive for COVID-19.^{19,20} The COVID-19 vaccination effectively reduces the incidence of critical and fatal cases. However, neonates cannot be vaccinated against COVID-19, have low immunity²¹ and, as a consequence, are vulnerable to epidemics. Infected newborns may die,²² and COVID-19 may also cause systemic diseases accompanied by multiple internal organ involvement.²³ Therefore, our understanding of COVID-19 should be deepened, and scientific countermeasures should be implemented to protect neonates.

Pregnant women are a high-risk group for COVID-19. Currently, studies on the effect of SARS-CoV-2 on neonatal outcomes are conflicting, and studies of COVID-19 in pregnancy are mostly limited to a single site with a small sample size and no appropriate control group.²⁴ Most studies have been carried out in urban areas, such as Wuhan and Shanghai, and studies focusing on newborns at high altitudes are scarce. The population in plateau regions lives in a chronic hypoxic environment, and previous studies show that a low-pressure and hypoxic environment affects foetal and neonatal health.²⁵ The oxygen concentration in the air has a significant effect on neonates infected with COVID-19, which may cause neonatal asphyxia, and critical patients with COVID-19 may rapidly progress to acute respiratory distress syndrome, septic shock, organ failure and even death.²⁶

Therefore, by focusing on neonates born to pregnant women infected with COVID-19, this study aims to deepen the understanding of the effect of pregnancy combined with COVID-19 on neonates and provide scientific evidence for early warning, prevention and treatment. The study is of great applicative significance for formulating disease prevention and control strategies and long-term birth plans for patients in the post-COVID era.

Research Participants and Methods

Research Participants

Cases of newborns born to pregnant women infected with COVID-19 who received prenatal care or treatment in the hospital between January 2020 and December 2022 were retrospectively collected (infected group) as well as newborns born to healthy pregnant women (non-infected group) included by age, underlying disease, and length of hospital stay. The above cases were from women and children in Tibet Autonomous Region Hospital and Lhasa People's Hospital. All eligible participants were included in chronological order according to the inclusion and exclusion criteria. All participants included in the infected group met the diagnostic criteria for laboratory and clinically confirmed cases of COVID-19 according to the Guidelines on the diagnosis and treatment of novel coronavirus pneumonia (trial version 5).²⁷ Inclusion criteria: pregnant women with or without COVID-19 aged 20–45 years. Exclusion criteria: patients with chromosomal abnormalities or congenital malformations of their reproductive organs. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Women and Children's Hospital of the Tibet Autonomous Region (qfeyy-2023001). Written informed consent was obtained from all parents and local guardians.

Birth malformations are defined as morphological or functional abnormalities in one or more parts of the body that appear during fetal development or after birth and are present at birth. For example, an organ or tissue is abnormal in shape, size or location, or something is present that impacts the normal functioning of the organ or system. Birth anomalies vary from mild (no significant impact on life) to severe (requiring immediate medical intervention or long-term treatment). These malformations can affect various aspects of the body, including the heart, brain, limbs and face.²⁸

The diagnostic criteria for a pneumonia diagnosis and the treatment protocol for novel coronavirus infection (trial version 5) were: (1) a real-time fluorescent reverse transcription polymerase chain reaction detection of novel coronavirus nucleic acid positivity in respiratory specimens or blood specimens or (2) viral gene sequencing in respiratory specimens or blood specimens, highly homologous to known novel coronavirus. Those with one of the above etiological pieces of evidence were included as confirmed cases.

Data Collection

The pregnancy outcome data, including basic neonatal information, the Apgar score at 1, 5 and 10 min, the neonatal intensive care unit (NICU) admission rate, neonatal mortality and neonatal complications, were collected from the two groups of pregnant women by consulting the electronic medical record information system or prenatal examination records. Specially trained attending physicians, obstetricians and gynaecologists with professional titles collected the above data, and all collected data were entered and verified by two individuals to ensure the validity of the data.

The basic information included sex, birth weight and length.

Apgar scoring was used to evaluate neonatal asphyxia.²⁹ After birth, newborns were scored according to five signs: skin colour, heart rate, respiration, muscle tone and movement and reflexes. Pale skin colour was scored 0, cyanotic skin 1 and ruddy skin 2. A score of 2 was given for a heart rate of more than 100 beats per min, 1 for less than 100 beats per min and 0 for no heart rate. Regarding respiration, irregular breathing or an “unloud” cry was scored 1, regular breathing and a loud cry 2 and no breathing 0. Good muscle tone was scored 2, decreased muscle tone 1 and floppy or no muscle tone 0. After the baby’s soles of the feet or nasal cannula were rubbed by hand, the baby developed crying, sneezing or coughing with a score of 2, and only slight reactions such as frowning with a score of 1 and no reactions with a score of 0. A total score of 8–10 was normal; 4–7 indicated mild asphyxia, also clinically known as asphyxia, requiring measures such as airway clearance, artificial respiration, oxygen inhalation and drug therapy; and 0–3 indicated severe asphyxia, also known as pale asphyxia, pointing to severe hypoxia requiring emergency treatment, such as laryngoscopic endotracheal intubation and oxygen inhalation under direct vision.

Neonatal complications included birth deformity, shortness of breath, moaning, irregular breathing and neonatal jaundice.

Evaluation Indicators

Primary outcome measures: the Apgar score at 1, 5 and 10 min.

Secondary outcome measures: the NICU admission rate, neonatal mortality and neonatal complications.

Statistical Analysis

Excel 2019 was applied for data compilation, and SPSS 26.00 for statistical analysis. Normally distributed or approximately normally distributed data were presented as $\bar{x} \pm s$, comparisons between the groups were performed with *t*-tests, and repeated-measures data were analysed using repeated-measures analysis of variance (separate effects were required if there was an interaction between time and group, indicating that neonatal outcomes had changed automatically over time in both groups, and the main effects were analysed if there was no interaction). The enumeration data were described by the number of cases and rate, and comparisons between the groups were performed using the χ^2 test. Multivariate analysis was performed using binary logistic regression. Significant suspected risk factors identified in the univariate analysis were coded by whether the Apgar score was >8 min at 1 min after birth as the dependent variable (yes = 1, no = 0), and logistic regression analysis was performed. Table 1 presents the grouping and coding information, and raw values were entered for the quantitative data. A backward approach using partial maximum likelihood estimation techniques (the inclusion criterion was $P \leq 0.05$, and the exclusion criterion was $P \geq 0.10$) was applied to include or exclude these factors, and logistic regression analysis models were then constructed. The inspection level was $\alpha = 0.05$, and all tests were two-sided.

Results

Comparison of the Clinical Data of the Neonates from the Two Groups

A total of 178 women and 203 men were included in the infected group compared with 163 women and 151 men in the non-infected group. In the infected group, birth weight was $3,201 \pm 532$ g and body length was 48.61 ± 2.31 cm; in the non-infected group, birth weight was $3,195 \pm 622$ g and body length was 49.36 ± 1.47 cm.

The two groups of neonates showed no statistically significant differences in sex, birth weight, body length, rates of NICU admission, neonatal mortality and birth deformity ($P > 0.05$). The differences in the neonatal Apgar scores

Table 1 Variable Grouping and Encoding

Variable	Grouping	Value
NICU admission	Yes	1
	No	2
Neonatal mortality	Yes	1
	No	2
Birth deformity	Yes	1
	No	2
Shortness of breath	Yes	1
	No	2
Moaning	Yes	1
	No	2
Irregular breathing	Yes	1
	No	2
Neonatal jaundice	Yes	1
	No	2

Abbreviation: NICU, neonatal intensive care unit.

($F_{treatment} = 231.351, P < 0.05$), rates of shortness of breath ($\chi^2 = 10.181, P < 0.05$), moaning ($\chi^2 = 6.132, P < 0.05$), irregular breathing ($\chi^2 = 8.346, P < 0.05$) and neonatal jaundice ($\chi^2 = 5.521, P < 0.05$) between the two groups were statistically significant, as shown in Table 2.

The interaction between the time*treatment of the neonatal Apgar scores of the two groups was not statistically significant ($F_{interaction} = 11.231, P > 0.05$), and, hence, the main effect was directly analysed. The neonatal Apgar scores of the two groups increased over time ($F_{time} = 112.471, P < 0.05$). Furthermore, the impact of whether a pregnant woman was infected with COVID-19 on the neonatal Apgar score varied ($F_{treatment} = 231.351, P < 0.05$). A further comparison of the magnitudes of the Apgar scores of the two groups of neonates at 1, 5 and 10 min showed that the non-infected group had a larger Apgar score at 1 min ($t = 3.478, P < 0.05$), 5 min ($t = 4.553, P < 0.05$) and 10 min ($t = 4.536, P < 0.05$).

Multivariate Analysis of Factors Influencing Neonatal Apgar Scores of the Two Groups

To further explore the factors influencing the Apgar scores, meaningful suspected risk factors were identified using binary logistic regression. The results showed that admission to NICU (OR = 3.342, 95% CI = 1.564–6.764, $P < 0.05$),

Table 2 Comparison of Clinical Data of Neonates from the Two Groups

Project	Infected Group (n=381)	Healthy Group (n=314)	χ^2/t value	P-value
Sex (male/female)	178/203	163/151	1.857	>0.05
Birth weight (g, $\bar{x}\pm s$)	3201.32±532.11	3195.43±621.55	0.983	>0.05
Body length (cm, $\bar{x}\pm s$)	48.61±2.31	49.36±1.47	0.996	>0.05
Apgar score ^a				
1min	7.91±0.96	8.35±1.01	3.478	<0.05
5min	8.46±0.99	8.96±1.11	4.553	<0.05
10min	9.01±1.10	9.44±1.07	4.536	<0.05
NICU admission (case)	3 (0.79)	2 (0.64)	0.055	>0.05
Neonatal mortality (case) ^b	2 (0.52)	0 (0)	-	0.504
Neonatal complications (case)				
Birth deformity	3 (0.79)	1(0.32)	0.584	>0.05
Shortness of breath	33 (8.66)	9 (2.87)	10.181	<0.05
Moaning	25 (6.56)	8 (2.55)	6.132	<0.05
Irregular breathing	13 (3.41)	1 (0.32)	8.346	<0.05
Neonatal jaundice	31 (8.14)	12 (3.82)	5.521	<0.05

Note: ^aAnalysis results of repeated measures variance $F_{treatment}=231.351, F_{time}=112.471, F_{interaction}=11.231$; ^bthe Fisher exact probability method was used.

Abbreviation: NICU, neonatal intensive care unit.

Table 3 Multivariate Analysis of Factors Influencing Neonatal Apgar Scores of the Two Groups

Variable	β	S.E	Wald	OR	95% CI	P-value
NICU admission	1.533	0.642	7.556	3.342	1.564~6.764	<0.05
Shortness of breath	1.434	0.689	8.143	2.853	1.789~3.154	<0.05
Moaning	1.542	0.698	0.744	1.596	0.897~1.897	>0.05
Irregular breathing	0.657	0.467	6.143	2.465	1.879~4.112	<0.05
Neonatal jaundice	1.422	0.498	6.316	2.324	1.989~2.445	<0.05

Abbreviation: NICU, neonatal intensive care unit.

shortness of breath (OR = 2.853, 95% CI = 1.789–3.154, $P < 0.05$), irregular breathing (OR = 2.465, 95% CI = 1.879–4.112, $P < 0.05$) and neonatal jaundice (OR = 2.324, 95% CI = 1.989–2.445, $P < 0.05$) were the factors influencing the low Apgar score in the infected group, as shown in Table 3.

Discussion

The results showed that the Apgar scores of newborns in the group of pregnant women infected with COVID-19 were lower than that of newborns in the non-infected group, and the incidence of complications, such as shortness of breath, groaning, irregular breathing and neonatal jaundice, was higher. Admission to the NICU, shortness of breath, irregular breathing and neonatal jaundice were the factors influencing the low Apgar scores of the neonates in the infected group. In this study, we investigated newborns living at high altitudes and proposed new findings to help improve the prognosis of newborns born to pregnant women infected with COVID-19. However, this study only looked at the short-term adverse effects of COVID-19 on pregnant women and newborns, and long-term follow-up and monitoring are necessary to further explore the long-term effects of SARS-CoV-2 on pregnant women and their offspring.

In this study, the group of pregnant women infected with COVID-19 had lower neonatal scores than the non-infected group, consistent with previous studies.³⁰ However, no differences in the lengths and weights of neonates were found. A study on perinatal and neonatal outcomes in pregnant women³⁰ showed that pregnant women with viral pneumonia were more likely to deliver newborns small for their gestational ages with low birth weights, foetal growth restrictions, preterm deliveries and low neonatal Apgar scores. This may be because women's unique hormonal and physiological alterations during pregnancy render their bodies more susceptible to respiratory pathogens and severe pneumonia.^{8,31} Possible mechanisms of action include changes in the maternal immune system during pregnancy (eg changes in Cd4 + T cells from a Th1 phenotype to a Th2 phenotype, decreases in circulating natural killer cells, increases in circulating progesterone levels and changes in the innate immune system),³² physiological changes in the respiratory system (uterine changes during pregnancy lead to diaphragmatic elevations and respiratory changes that increase susceptibility to respiratory infections)³³ and changes in coagulation (a hypercoagulable state during pregnancy).³⁴ Compared with previous studies of pregnant women infected with SARS, MERS and influenza A virus subtype, H1N1,¹³ pregnant women infected with COVID-19 had a higher incidence of neonatal outcomes. Therefore, the pathogenic mechanisms responsible for the adverse neonatal outcomes caused by SARS-CoV-2 in pregnant women and newborns should be investigated further to identify targeted prevention and treatment strategies.

In this study, most neonates had evident jaundice symptoms. Studies^{35,36} show that COVID-19 affects the liver and gastrointestinal system, possibly causing neonatal isoerythrolysis and excessive bilirubin generation, which requires further research. The physiological basis of children's low susceptibility also plays a role. The main target sites³⁷ of SARS-CoV-2 when infecting humans are ACE2 receptors. Most neonatal cases had mild symptoms, which may be attributed to their low function or expression of ACE2 receptors that limit the virus entry pathways.³⁸

In this study, newborns born to pregnant women in the group infected with COVID-19 had a higher incidence of shortness of breath, groaning and irregular breathing. Multivariate analysis also showed that admission to the NICU, shortness of breath and irregular breathing were risk factors for low Apgar scores. Li Zewu et al³⁹ reported that the mortality rate of pregnant women and their foetuses infected with the novel coronavirus was low but that the adverse pregnancy outcome or pregnancy complication rate was significantly increased, including premature delivery, low birth

weight, premature rupture of membranes and foetal distress. This suggests that we should give timely individualised intervention to pregnant women infected with SARS-CoV-2 according to the severity of the disease and pregnancy progression, with more attention paid to pregnant women infected with SARS-CoV-2 in the first and second trimesters to prevent the occurrence of adverse outcomes.

This study has some limitations. First, this is a retrospective study with patients from multiple research centres, with the differences in electronic record systems resulting in a loss of clinical data for some of the patients. Second, patients' willingness to undergo prenatal examinations was low during the pandemic, and some of the patients were lost to follow-up, which resulted in a failure to obtain continuous data. Third, some neonates born in the early stage of the epidemic did not receive SARS-CoV-2 nucleic acid and antibody tests. Fourth, the number of patients in early and mid-term pregnancy was small, and a larger number of samples are needed to explore the effect of SARS-CoV-2 on pregnant women in these stages. Fifth, this study failed to collect and test the breast milk, vaginal fluid and intrauterine tissue samples of some of the patients, making it difficult to confirm the presence of mother-to-child transmission. Sixth, most patients with mild symptoms were treated at mobile cabin hospitals or other public facilities, whereas pregnant women infected with COVID-19 were hospitalised in designated institutions, which may have caused selection bias in the incorporation of the group of pregnant women infected with COVID-19.

Conclusion

Neonates born to pregnant women infected with COVID-19 had lower Apgar scores and a higher incidence of complications, such as shortness of breath, groaning, irregular breathing and neonatal jaundice than newborns born to pregnant women in the non-infected group. Clinically, attention should be given to the physical condition of newborns born to women infected with COVID-19, and monitoring should be strengthened, with particular attention paid to the respiratory status of newborns, timely optimisation of treatment options and improvement in prognosis.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Women and Children's Hospital of Tibet Autonomous Region (qfeyy-202300). Written informed consent was obtained from all parents/local guardians.

Funding

Tibet Autonomous Region Key R&D Project (XZ202201ZY0044G).

Disclosure

None of the authors have any personal, financial, commercial, or academic conflicts of interest to report for this work.

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