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The association of increased incidence of congenital heart disease in newborns with maternal COVID-19 infection during pregnancy

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This paper aims to examine the potential link between maternal COVID-19 infection during pregnancy and the increased risk of congenital heart disease (CHD) in newborns. A comparative analysis was conducted involving two groups: mothers infected with COVID-19 during pregnancy and a control group. Data on maternal characteristics, pregnancy-related complications, and newborn outcomes were collected and analyzed. Additionally, the annual incidence rates of CHD from 2020 to 2023 were evaluated to assess trends over time. No significant differences were found between the COVID-19 cases and the control group in terms of maternal age, BMI, gravidity, parity, use of assisted reproductive technology, adverse obstetric history, or complications during pregnancy, including diabetes mellitus, preeclampsia, and thyroid abnormalities. For newborn outcomes, there were no significant differences in sex distribution, rate of cesarean delivery, Apgar scores, or birth weight. However, a significantly higher prevalence of cardiac ultrasound abnormalities was observed in the COVID-19 group (10.08%) compared to the control group (4.13%, $p = 0.012$). Further analysis revealed that the majority of cardiac abnormalities in the COVID-19 group occurred in mothers infected before 8 weeks of pregnancy. The annual incidence rates of CHD showed a significant increase during the COVID-19 pandemic, with the highest rate in 2023 (5.46%) compared to previous years. Maternal COVID-19 infection during pregnancy may adversely affect the development of the newborn's heart. This could be due to the inflammatory response caused by the viral infection or other pathological processes. The findings underscore the importance of vigilant prenatal care and early detection of cardiac abnormalities during the pandemic and suggest the need for further research to explore potential mechanisms and intervention strategies.

Keywords COVID-19, Pregnancy infection, Congenital heart disease, Newborns, Risk factors

COVID-19, resulting from the SARS-CoV-2 virus, became a global pandemic in early 2020, impacting millions of individuals worldwide. The disease is characterized by a wide range of symptoms, ranging from mild respiratory issues to severe acute respiratory distress syndrome (ARDS) and multi-organ failure. Its impact on healthcare systems, economies, and daily life has been profound, necessitating unprecedented public health measures[1,2]. Research into the effects of maternal COVID-19 infection on pregnant women and their newborns is increasing.

As a particularly vulnerable population, COVID-19 presents unique challenges and risks for pregnant individuals. While initial studies suggested that pregnant women might not face a higher risk of severe illness compared to the general population[3], later research indicated a higher risk of severe outcomes. For the mother, COVID-19 infection may exacerbate respiratory symptoms and increase the risk of preterm birth and cesarean delivery. For the fetus, COVID-19 infection may lead to adverse birth outcomes[4]. Viral infections during the early stages of pregnancy can cause congenital defects in newborns due to functional changes in early embryonic

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cells, such as varicella and rubella[5]. However, there is limited information on the incidence of congenital defects in newborns of mothers infected with COVID-19, necessitating further investigation.

In the early stages of the COVID-19 pandemic, China implemented stringent lockdowns and quarantine policies across the country, resulting in a very low infection rate. As the pandemic came under greater control and the virulence of the virus appeared to decrease, China adjusted its pandemic control strategies. At the end of 2022, the Chinese government announced a relaxation of its COVID-19 prevention measures, entering a phase of "coexisting with the virus." This transition was followed by a significant rise in infection rates.

In 2023, we observed an increase in CHD among newborns, prompting the initiation of this study. Our study focuses on the pregnant women who became infected during this phase. While significant research has focused on the general effects of COVID-19 on pregnancy, there remains a paucity of data specifically addressing its impact on neonatal heart abnormalities[6]. Understanding these outcomes is crucial, given the potential long-term implications for infant health. This study aims to compare the basic characteristics and pregnancy-related complications of mothers infected with COVID-19 during pregnancy to a control group, as well as to evaluate the characteristics and outcomes of their newborns, with a specific focus on the incidence and types of CHD. Additionally, we analyze the annual incidence rates of CHD in newborns over the past four years, including during the COVID-19 pandemic.

Materials and methods

Study design and participants

This retrospective study was conducted among newborns and their mothers who gave birth between January 2023 and December 2023 at the Shanxi Province Integrated Traditional and Western Medicine Hospital. The study population consisted of pregnant women who were infected with COVID-19 during their pregnancy (COVID-19 group) and a control group of pregnant women who were not infected with COVID-19. The COVID-19 group included women with confirmed SARS-CoV-2 infection, diagnosed via RT-PCR testing from nasopharyngeal swabs, at any point during their pregnancy. The control group comprised pregnant women without any documented COVID-19 infection. All newborns with abnormal cardiac auscultation findings underwent an echocardiographic examination, which was performed after 72 h postnatally. Cardiac development was evaluated by a radiologist with an echocardiographic examination. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and received approval from the ethical committee of the Shanxi Integrative Medicine Hospital.

Data collection

Data were collected from electronic medical records and included maternal demographics, pregnancy-related complications, delivery outcomes, and neonatal characteristics. Maternal demographics included age, BMI, gravidity, and parity. Pregnancy-related complications recorded included the use of assisted reproductive technology (ART), adverse obstetric history, diabetes mellitus, preeclampsia, and thyroid abnormalities. Regarding the vaccination status, all the pregnant women in our study had received their COVID-19 vaccination prior to pregnancy.

Neonatal characteristics and outcomes assessed were sex, mode of delivery (cesarean or vaginal), Apgar scores at 1 and 5 min, birth weight, and the presence of cardiac abnormalities detected by ultrasound. Cardiac abnormalities analyzed included atrial septal defects (ASD), patent foramen ovale (PFO), ventricular septal defects (VSD), and patent ductus arteriosus (PDA). Additionally, the annual incidence rates of CHD from 2020 to 2023 were evaluated.

Statistical analyses

Statistical analysis was performed using SPSS 26.0. The Shapiro-Wilk and Kolmogorov-Smirnov tests checked if continuous variables were normally distributed. If they were, data were presented as mean ± standard deviation (SD). For non-normally distributed data, the median with interquartile range (IQR) was used. Categorical variables were expressed as frequencies and percentages. The independent t-test or Mann-Whitney U test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables between the COVID-19 group and the control group. The incidence rates of CHD over the four years were calculated and compared. Statistical significance was set at $p < 0.05$.

Results

Comparison of general information of maternal between two groups

A comparative analysis was conducted to assess the basic characteristics and pregnancy-related complications between maternal infected with COVID-19 during pregnancy and a control group. As summarized in Table 1.

The analysis revealed no statistically significant differences between the COVID-19 cases and the control group in terms of age ($p = 0.254$) and BMI ($p = 0.986$). Gravidity and parity also showed similar distributions between the groups, with median values of 2 (IQR: 1–3) and 1 (IQR: 1–2), respectively, with p-values of 0.766 and 0.747. The prevalence of ART use was slightly higher in the COVID-19 cases (4.20%) compared to the control group (2.91%), though this difference was not statistically significant ($p = 0.553$). Similarly, adverse obstetric history was observed in 1.68% of the COVID-19 cases and 3.16% of the controls, with no significant difference ($p = 0.539$). In terms of complications during pregnancy, the occurrence of diabetes mellitus ($p = 0.352$), preeclampsia ($p = 0.103$), and thyroid abnormalities ($p = 0.840$) did not differ significantly between the COVID-19 cases and the control group.

	COVID-19 cases ($n=119$)	Control ($n=412$)	P
Age (years)	30.93 ± 3.81	31.41 ± 4.02	0.254
BMI(Kg/m^2)	27.95 ± 3.49	27.98 ± 3.67	0.986
Gravidity(median, IQR)	2(1–3)	2(1–3)	0.766
Parity(median, IQR)	1(1–2)	1(1–2)	0.747
ART	5(4.20%)	12(2.91%)	0.553
Adverse obstetric history	2(1.68%)	13(3.16%)	0.539
Complications during pregnancy			
Diabetes mellitus	24(20.17%)	68(16.5%)	0.352
Preeclampsia	7(5.88%)	45(10.92%)	0.103
Thyroid abnormalities	19(15.67%)	69(16.75%)	0.840

Table 1. Comparison of basic characteristics and pregnancy complications. Data are given as mean ± SD, median (IQR) or n (%). *Bold values indicate statistically significant $p<0.05$. ART: Assisted Reproductive Technology.

Newborns	COVID-19 cases ($n=119$)	Control ($n=412$)	P
Sex (female)	59(49.58%)	190(46.11%)	0.505
Cesarean delivery	58(48.74%)	189(45.87%)	0.588
Apgar score at 1 min	10(7–10)	10(4–10)	0.060
Apgar score at 5 min	10(7–10)	10(6–10)	0.121
Birth weight(grams)	3213.61 ± 497.58	3253.16 ± 431.94	0.225
Cardiac ultrasound abnormalities	12(10%)	17(4.13%)	**0.012***
Premature birth	9(8.18%)	17(4.13%)	0.126

Table 2. Comparison of newborn characteristics and outcomes. Data are given as mean ± SD, median (IQR) or n (%). *Bold values indicate statistically significant $p<0.05$.

Cardiac Abnormality	COVID-19 Cases ($n=12$)	Control ($n=17$)	P
Atrial septal defect (ASD)	8	2	<0.001
Patent foramen ovale (PFO)	6	15	
Ventricular septal defect (VSD)	2	2	
Patent ductus arteriosus (PDA)	3	10	

Table 3. Types of cardiac abnormalities in newborns.

Comparison of newborn characteristics and outcomes between two groups

A comparative analysis was also conducted to assess the characteristics and outcomes of newborns between the two groups. The data are summarized in Table 2. The analysis revealed no statistically significant differences between the COVID-19 cases and the control group in terms of the sex distribution of the newborns ($p=0.505$) and the rate of cesarean delivery ($p=0.588$). The Apgar scores at 1 min and 5 min were also similar between the groups, with median (min-max) values of 10 (7–10) and 10 (4–10) at 1 min ($p=0.060$) and 10 (7–10) and 10 (6–10) at 5 min ($p=0.121$) for the COVID-19 and control groups, respectively.

Birth weight showed no significant difference between the newborns of COVID-19-infected individuals and the control group ($p=0.225$). However, a statistically significant difference was observed in the prevalence of cardiac ultrasound abnormalities, with 10.08% of the newborns in the COVID-19 group exhibiting abnormalities compared to 4.13% in the control group ($p=0.012$). The rate of premature birth was higher in the COVID-19 group (8.18%) compared to the control group (4.13%), but this difference did not reach statistical significance ($p=0.126$).

Characteristics of CHD in newborns

Further analysis was conducted on the 12 newborns with cardiac abnormalities in the COVID-19 infection group. We found that 11 of these cases involved mothers who were infected before 8 weeks of pregnancy, while one case involved infection at 23 weeks of pregnancy. The specific types of cardiac abnormalities observed in the COVID-19 infection group included ASD in 8 cases, PFO in 6 cases, VSD in 2 cases, and PDA in 3 cases.

In the control group, there were 17 newborns with cardiac abnormalities. The most common abnormality was PFO, observed in 15 cases, followed by PDA in 10 cases, VSD in 2 cases, and ASD in 2 cases. The distribution of cardiac abnormalities between the two groups is summarized in Table 3.

Annual incidence rates of CHD in newborns

In addition to the comparison of newborn characteristics and outcomes between COVID-19 cases and controls, we analyzed the prevalence of CHD in newborns at our hospital over the past four years, including during the COVID-19 pandemic. The annual incidence rates of CHD from 2020 to 2023 are illustrated in Fig. 1.

The data demonstrate an increasing trend in the incidence of CHD over the four years, with a notable rise during the COVID-19 pandemic in 2023. The incidence rate of CHD in 2023, during the COVID-19 pandemic, was significantly higher at 5.46% compared to previous years. Specifically, the incidence rates were 1.12% in 2020, 2.36% in 2021, and 3.87% in 2022 ($p<0.001$). In addition, our data indicate a significant downward trend in the number of newborns.

Discussion

Given the evolving nature of the COVID-19 pandemic, ongoing research and data collection are essential to understand its full impact on pregnant women and to develop evidence-based guidelines for their care. Public health policies should continue to address the unique needs of this population to ensure both maternal and child health. CHD are common birth defect in newborns, including ASD, VSD, and PDA. These abnormalities can affect a child's normal development and have long-term health implications. Early studies indicate that maternal COVID-19 infection during pregnancy may result in several complications, such as pregnancy-induced hypertension preterm birth, and fetal growth restriction[7].

In our study, the absence of significant differences in basic maternal characteristics and most pregnancy-related complications between the COVID-19 and control groups may be due to differences in study methodology. Our study retrospectively analyzed mothers' COVID-19 infection status during pregnancy based on their newborns, excluding women who experienced severe pregnancy complications resulting in fetal death. Another possible reason is that by the time China's COVID-19 restrictions were lifted in 2022, the virulence of the virus had diminished.

We have also evaluated the characteristics and outcomes of newborns from individuals infected with COVID-19 and a control group. Our findings revealed no statistically significant differences in several key parameters, including the sex distribution of the newborns, the rate of cesarean delivery, Apgar scores, and birth weight. This finding suggests that COVID-19 infection does not preferentially affect these neonatal outcomes, consistent with other studies that have reported similar outcomes[8]. While some earlier studies have reported higher cesarean delivery rates and intrauterine growth restriction among COVID-19-positive mothers, due to concerns about respiratory complications, fetal distress, and severe cases of maternal COVID-19[9,10].

Despite the absence of significant differences in basic maternal characteristics and most pregnancy-related complications between the COVID-19 and control groups, a notable exception was the significantly higher incidence of CHD in newborns of mothers infected with COVID-19. This result suggests a possible link between maternal COVID-19 infection and a heightened susceptibility to CHD in newborns. There are currently a few other studies that have reached similar conclusions. Mohamed et al. reported a case in which a 34-years-old non-vaccinated pregnant woman who contracted COVID-19 in the early stages of pregnancy delivered prematurely at 34 weeks, with the fetus exhibiting congenital heart defects, indicating a potential influence of COVID-19 on the onset of such abnormalities[11]. Another study on prenatal diagnostics in pregnant women infected with the novel coronavirus during pregnancy found that the frequency of congenital anomalies in fetuses was 13.8%, with cardiovascular anomalies being the second most common congenital malformation after facial anomalies[12].

However, the specific mechanisms by which COVID-19 may influence fetal heart development remain unclear and require further research. Possible mechanisms could include viral-induced inflammatory responses

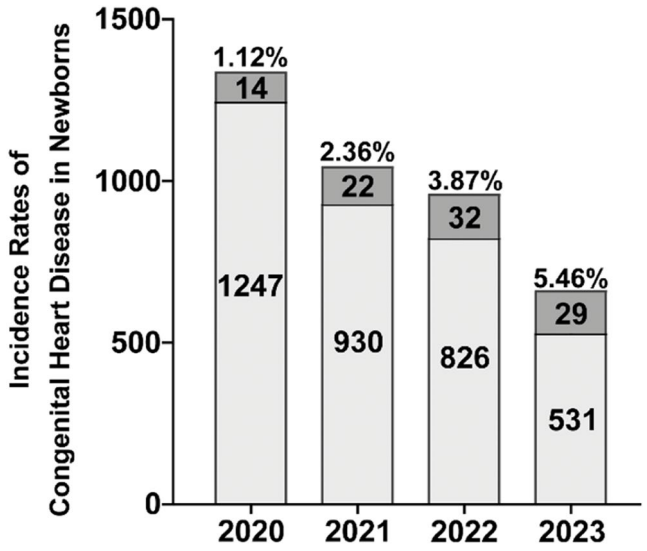

Figure 1. Incidence rates of congenital heart disease in newborns (2020–2023).

or direct viral effects on fetal cardiac tissue[13]. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and spike protein protease receptors for cell entry. These receptors are found highly expressed in maternal-fetal interface cells and multiple fetal organs, indicating a potential pathway for the virus to infect fetal cells and disrupt development[14]. This theory could explain the mechanism of SARS-CoV-2 transmission from mother to fetus during early pregnancy.

Recent studies have also indicated that COVID-19 infection may be potentially associated with congenital malformations and fetal arrhythmia[15,16]. Even in the absence of direct effects on the standard growth and development of the embryo, COVID-19 infection-related factors may indirectly pose risks to the fetus. These factors encompass diminished access to prenatal care due to pandemic-related restrictions, financial challenges stemming from the pandemic and ensuing lockdowns, and restricted avenues for fetal screening and diagnosis, particularly amid widespread health emergencies[15]. This highlights the need for careful monitoring of newborns from COVID-19-positive mothers. However, some studies have not identified any neurological or cardiac teratogenic effects associated with COVID-19 infection during pregnancy[17,18]. Our results still require further extensive research to be validated.

In the COVID-19 infection group, another notable finding was that 11 out of 12 cases of cardiac abnormalities occurred in mothers who contracted the virus before 8 weeks of gestation. The heart is among the first organs to develop during embryogenesis. By the seventh week of gestation, the four chambers are fully formed[19]. If the endocardial cushions fail to fuse during this phase, it can lead to the development of an atrioventricular septal defect (AVSD)[20]. Additionally, other viral infections during early pregnancy, such as rubella, are known to cause specific congenital anomaly syndromes. A meta-analysis revealed that viral infections in early pregnancy, such as rubella and cytomegalovirus, substantially increase the risk of CHD in the offspring compared to mothers without such infections[21]. This suggests a possible critical period during early pregnancy where exposure to the virus may have a greater impact on cardiac development.

The predominance of ASD in the COVID-19 group, as opposed to the control group where PFO was more common, may indicate specific vulnerabilities in cardiac development associated with early gestational COVID-19 infection. The primary risk factors for complete ASD are diabetes mellitus, smoking, alcohol, Down syndrome, rubella or other viral infections, and certain medications[11]. The lack of additional risk factors aside from COVID-19 infection at the onset of pregnancy prompted us to hypothesize a potential association between the virus and congenital abnormalities, particularly ASD. The differences in the types of cardiac abnormalities observed between the COVID-19 infection group and the control group also raise important questions. For instance, the higher incidence of ASD in the COVID-19 group contrasts with the control group, where PFO and PDA were more prevalent. This variation could be due to the direct effects of the virus on fetal cardiac development or an indirect effect mediated through the maternal immune response or other related factors[16].

Additionally, we investigated the annual incidence rates of CHD from 2020 to 2023, highlighting a significant increase during the COVID-19 pandemic, particularly in 2023, reaching 5.46%. Currently, there are few reports of neonatal cardiac abnormalities during the COVID-19 pandemic. A study based on the "Iranian Maternal and Neonatal" (IMaN) Network revealed a notable rise in the incidence of congenital birth anomalies during the COVID-19 pandemic in comparison to the pre-pandemic period ($P<0.00001$)[22]. Furthermore, the increased incidence of CHD observed in our study during the pandemic may also reflect broader healthcare system disruptions and reduced prenatal care during this period. The pandemic has led to significant changes in healthcare delivery, with many pregnant individuals experiencing delays in receiving routine prenatal screening and care[23]. This reduced access to prenatal care could result in a higher incidence of undiagnosed and subsequently untreated conditions, potentially contributing to the observed rise in congenital birth anomalies.

Furthermore, studies have demonstrated that all congenital anomalies, particularly congenital heart defects, are associated with increased COVID-19 severity in pediatric patients[24]. Recognizing the effects of SARS-CoV-2 infection on fetuses during early pregnancy is essential for addressing potential fetal defects and minimizing neonatal morbidity. Thus, we suggest a plausible association between maternal COVID-19 infection at the beginning of pregnancy and the occurrence of congenital heart anomalies in the fetus. While our study provides valuable insights, it is limited by the retrospective nature of the data and potential confounding factors that were not fully accounted for. Future research should focus on prospective studies and larger sample sizes to confirm these findings and explore the biological mechanisms in more detail. Investigating the long-term outcomes of children born to COVID-19-infected mothers will also be crucial in understanding the full impact of the virus on child health.

In conclusion, the significant increase in congenital abnormalities during the COVID-19 pandemic, particularly the early gestational infections associated with specific types of cardiac abnormalities, emphasizes the need for ongoing monitoring and support for children born during the pandemic. Further research is essential to confirm these results and to develop effective interventions to protect maternal and child health in the face of future public health challenges.

Data availability

All data relevant to this study are provided within the published article. For additional inquiries, please contact the corresponding author.

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Author contributions

Huimin Ren, Xianhui Zhang, and Sufeng Zhang were involved in data collection, analysis, and the initial drafting of the manuscript. Jie Pan and Wei Wang contributed to the study's conception and design. Wei Wang provided supervision, edited, and revised the article.

Declarations

Ethics statement

The study received ethical approval from the Shanxi Integrative Medicine Hospital's ethics committee. Given the retrospective nature of the study, the requirement for informed consent was waived by the ethical committee of the Shanxi Integrative Medicine Hospital from the participant's or their legal guardians.

Competing interests

The authors declare no competing interests.

Additional information

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