Cardiology in the Young

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The incidence and risk factors of fetuses with mirror-image dextrocardia with solitus inversus

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Abstract

Objective: This research seeks to ascertain the prevalence and determinants of mirror-image dextrocardia in fetuses *Study design:* With December 2022 as the reference point, we compiled colleted data on pregnant women who carried fetuses with mirror-image dextrocardia in Xi'an, Shaanxi Province: September–October 2022, November 2022, and December 2022–January 2023. An online questionnaire was distributed to 209 pregnant across China who had contracted COVID-19. The case group comprised women whose final menstrual cycle occurred in November 2022 and who had a fetus with mirror-image dextrocardia. Women with a November 2022 final menstrual period and a fetus without this condition made up the control group. To identify the risk factors associated with fetal mirror-image dextrocardia, both univariate and multivariate logistic regression analyses were employed. *Results:* A significant difference was noted in the gestational age at COVID-19 infection women with a September to October 2022 and December 2022 to January 2023 final menstrual period who did not bear a fetus with mirror-image dextrocardia, and those with a November 2022 final menstrual period whose fetus exhibited this condition. The univariate and multivariate analyses conducted on pregnant women with a final menstrual period in November 2022 who had contracted COVID-19 revealed significant differences in the presence and duration of fever between those bearing fetuses with mirror-image dextrocardia and those without ($P = 0.000$). *Conclusion:* The findings suggest two critical factors to the increased prevalence of fetal mirror-image dextrocardia: 1) the infection timing which occurs between the 4th and 6th week of pregnancy and 2) the presence of fever and its prolonged duration.

Introduction

Mirror-image dextrocardia, a rare condition, is reported to have an incidence rate of 1 in 10,000 according to literature.[1,2]The diagnosis of fetal situs primarily relies on ultrasonography, and its characteristic manifestations are as follows: first, the heart axis of the fetus points towards the right, with the apex of the heart located in the right chest cavity and pointing towards the right. At this time, the internal organs undergo transposition, and the positions of the atria, ventricles, and large blood vessels are all opposite to those of a normal left-sided heart, resembling a mirror image. Despite the change in the position of the heart, the connection relationship of the major blood vessels of the heart remains normal. Second, in the four-chamber heart section, the specific position of the apex of the heart pointing to the fetal chest can be observed. For instance, when the fetus is in the left occiput position, the apex of the heart points to approximately the 10 o'clock position of the fetal chest, with the left atrium and left ventricle close to the probe side, while the right atrium and right ventricle are far away from the probe side. Further studies by Pradegan N and others suggest an approximate incidence of 1 in 12,000 among adults.[3,4] Bohun CM and colleagues found that the incidence rate during pregnancy is slightly lower at 0.8 in 10,000.[1] An estimation by Rajesh V and team indicates a prevalence rate of 1.2 in 10,000 across all age groups and a higher rate in newborns at 2.9 in 10,000.[5]

Our previous research revealed that the incidence of mirror-image dextrocardia in pregnant women who underwent prenatal ultrasound in three hospitals in Shaanxi Province between 2019 and 2023 was 2.2 in 10,000, 0.9 in 10,000, and 18.2 in 10,000, respectively. This data signals a sharp increase in the incidence of this condition during the COVID-19 pandemic in Shaanxi Province. Moreover, we distributed a nationwide questionnaire to pregnant women who had contracted COVID-19 and received a fetal diagnosis of mirror-image dextrocardia. The results showed that the majority of these women had their last menstrual period in November 2022 and had a shared experience: they all contracted COVID-19 during the gestational period of 4–6 weeks in December 2022. Based on these findings, we sought to investigate the following: if the incidence of fetal mirror-image dextrocardia increases among women with last menstrual

period in November and a COVID-19 infection at 4–6 weeks gestation, what is the incidence in women who became pregnant either before or after November 2022? Are there external factors, beyond the timing of the last menstrual period and the time of COVID-19 infection, that could impact this? Therefore, we included pregnant women who had their last menstrual period before the COVID-19 outbreak in September to October of 2022, those who had their last menstrual period in November and those who had their last menstrual period after the pandemic in December 2022. We aimed to compare the incidence of fetal mirror-image dextrocardia among these groups.

In addition, we developed a survey focusing on risk factors for fetal mirror-image dextrocardia. This survey was administered online to pregnant women with COVID-19 and a fetal diagnosis of mirror-image dextrocardia, as well as those who had contracted COVID-19 but did not have a fetus with this condition. The primary objective of this study was to identify the risk factors that contributed to the sharp increase in the incidence of fetal mirror-image dextrocardia following the COVID-19 pandemic.

Materials and methods

Study population

This study included pregnant women treated at the Xi'an International Medical Center Hospital, Northwest Women's and Children's Hospital, and Xi'an Angel Women's & Children's Hospital between 2022 and 2023. These women had their last menstrual period within one of three specific timeframes: September 1 to October 31 of 2022, November 1 to 30 of 2022, and December 1, 2022 to January 31, 2023. All of these women were diagnosed with fetal mirror-image dextrocardia due to COVID-19 infection.

On a national scale, we focused on pregnant women whose last menstrual period was in November 2022. We divided these women into two groups: those diagnosed with fetal mirror-image dextrocardia (case group) and those without this diagnosis (control group). The case group consisted of 106 individuals, while the control group included 103 individuals. Every participant provided informed consent to participate in this study. The Ethics Committee of Xi'an International Medical Center Hospital approved the research protocol.

Epidemiological survey

A comprehensive, scientifically structured epidemiological questionnaire was designed for the study, with the following categories:

(1) General Information: This section captures details about the pregnant woman such as name, couple's age, city and province of residence, date of last menstrual period, date of initial pregnancy detection, obstetric history, conception method, expected delivery date, and gestational age at the time of COVID-19 infection. The gestational age is divided into four categories: not pregnant at the time of COVID-19 infection, gestational age <4 weeks, 4 weeks ≤ gestational age ≤ 6 weeks, and gestational age >6 weeks.
(2) COVID-19 Infection Status: This portion records whether the participant was infected with COVID-19, results of nucleic acid tests, presence and peak body temperature if feverish (segmented into four categories: low-grade fever 37.4–38° C, moderate fever 38.1–39 °C, high fever 39.1–41 °C, ultra-high fever ≥41 °C), duration of fever (categorised into: $t \leq 24$ h, 24 h$< t \leq 72$ h, $t > 72$ h), and symptoms such as cough with or without expectoration, sore throat, diarrhoea, loss of taste, drowsiness, systemic soreness, fatigue, chest tightness, shortness of breath, and nasal congestion or discharge.
(3) Pregnancy Comorbidities: This includes presence or absence of conditions like diabetes mellitus, hypertension, hyperlipidemia, and thyroid disease.
(4) Medication History During Pregnancy: This section asks whether the participant has taken any antipyretic analgesics, such as fever-reducing drugs or cold medicine.
(5) Vaccination History: This part records if the participant has received any vaccinations and if so, recorded which type of vaccine and time of vaccination.
(6) Lifestyle Habits: This captures information on smoking and drinking habits.
(7) Family History: This asks whether there is a family history of hereditary diseases, mirror-image right-sided heart disease, or consanguineous marriage.
(8) Environmental Exposure: This seeks to record information on pet ownership, home renovations during the 3 months prior to pregnancy, exposure to toxic or harmful substances, and encounters with adverse environments.

Statistical analysis

Data were collated into a database and analysed using the SPSS 27.0 software. Categorical data were expressed as frequencies and percentages (%). Chi-square (χ^2) test was employed for univariate analysis, while multivariate logistic regression analysis was performed to identify risk factors associated with fetal mirror-image dextrocardia. R software was utilised to generate forest plots for visual representation of the results.

Results

Screening was performed on pregnant women who underwent ultrasound examinations at the Ultrasound Department of Xi'an International Medical Center Hospital, Northwest Women's and Children's Hospital, and Xi'an Angel Women's & Children's Hospital. Their last menstrual periods fell within three distinct time intervals: September–October 2022, November 2022, and December 2022–January 2023. In total, 28 pregnant women with a history of COVID-19 infection and fetal mirror-image dextrocardia were identified. This included 2 cases from September–October 2022, 24 cases from November 2022, and 2 cases from December 2022–January 2023. The data revealed that the incidence of fetal mirror-image dextrocardia was significantly elevated in pregnant women whose last menstrual period occurred in November, compared to the preceding and following 2-month periods (Figure 1).

A variance analysis was performed comparing the gestational age at which pregnant women with their last menstrual period in September–October 2022, who did not have fetal mirror-image dextrocardia, were infected with COVID-19, versus the gestational age at which pregnant women with their last menstrual period in November 2022, who did have fetal mirror-image dextrocardia, were infected with COVID-19 (Table 1). It was found that 80.2% of women with fetal mirror-image dextrocardia were infected with COVID-19 during weeks 4–6 of pregnancy, while 93% of women without fetal mirror-image dextrocardia were infected with COVID-19 at a gestational age of greater than 6 weeks. There was a statistically significant difference in the gestational age at

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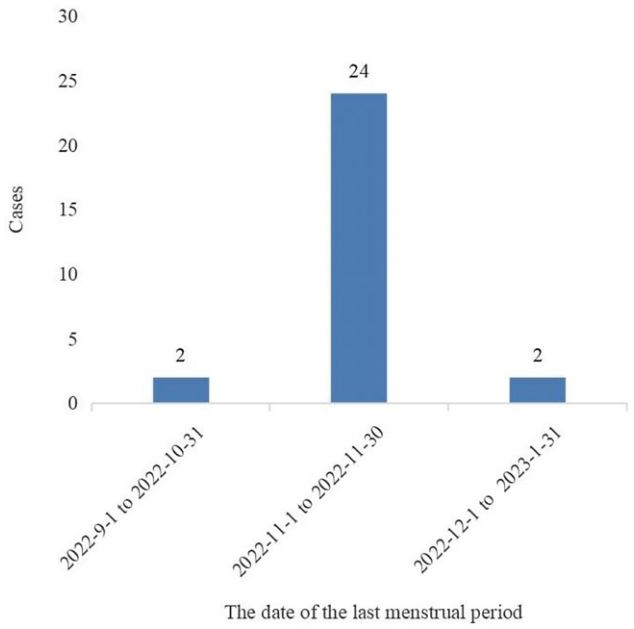

Figure 1. Number of fetuses with mirror dextrocardia during the last menstrual period from September to October 2022, November 2022 and December 2022 to January 2023 in four hospitals in Shaanxi Province.

which these two groups of pregnant women were infected with COVID-19 ($\chi^2 = 128.433$, $p < 0.001$), but without fetal mirror-image dextrocardia whose last menstrual period was in September–October 2022 and pregnant women with COVID-19 infection and with fetal mirror-image dextrocardia whose last menstrual period was in November 2022.

A variance analysis was performed comparing the gestational age at which pregnant women with their last menstrual period in December 2022–January 2023, who did not have fetal mirror-image dextrocardia, were infected with COVID-19, versus the gestational age at which pregnant women with their last menstrual period in November 2022, who did have fetal mirror-image dextrocardia, were infected with COVID-19 (Table 2). It was found that 80.2% of women with fetal mirror-image dextrocardia were infected with COVID-19 during weeks 4–6 of pregnancy, 68.6% of the pregnant women in the dextrocardia negative group were not pregnant when infected with COVID-19. There was a statistically significant difference in the gestational age at which these two groups of pregnant women were infected with COVID-19 ($\chi^2 = 176.537$, $p < 0.001$).

In conducting the single-factor analysis and multiple logistic regression analysis on risk factors for fetal mirror-image dextrocardia in China after the COVID-19 pandemic in December 2022, we assigned numerical values to each factor. The conception method was assigned as "natural" = 1 and "assisted" = 2. COVID-19 nucleic acid test results were categorised as "positive" = 1 and "negative" = 2, while other items were characterised as "yes" = 1 and "no" = 2. A logistic regression analysis table was then generated, and a forest plot was constructed to visualise these findings.

The single-factor analysis conducted on pregnant women with a history of COVID-19 infection but without fetal mirror-image dextrocardia (last menstrual period in November 2022) and pregnant women with a history of COVID-19 infection and with fetal mirror-image dextrocardia (last menstrual period in November 2022) revealed several independent risk factors for the occurrence of fetal mirror-image dextrocardia, including: presence of cough and sputum production, stuffy or runny nose, having thyroid disease, smoking habit, exposure to chemicals in the couple's occupation, home renovations or exposure to toxic and harmful substances during the first 3 months of pregnancy, highest body temperature during episodes of fever, duration of fever, number of vaccine doses administered, presence of fever, diarrhoea, and taste loss. These factors were tabulated (Table 3). Multiple logistic regression analysis was then performed on the independent risk factors obtained from the single-factor analysis, revealing that the highest body temperature during pregnancy and the duration of fever were significant risk factors for COVID-19-infected pregnant women developing fetal mirror-image dextrocardia (Figure 2, Table 4).

Discussion

Embryonic heart development primarily occurs during the first trimester, specifically between weeks 4 and 6, during which the primitive cardiovascular system develops rapidly. The system bends rightwards, positioning the right ventricle on the right and the left ventricle on the left. It also bends backwards, situating the ventricles in front and the atria behind. Additionally, it bends upwards, positioning the atria superiorly and the ventricles inferiorly. This establishes the basic morphological structure of the right ventricular loop of the heart. Interference during this critical period of heart development, due to certain factors, can cause the primitive cardiovascular system to bend leftwards, leading to the heart axis pointing to the lower right, with the heart apex located in the right chest, resulting in mirror-image dextrocardia.

After the COVID-19 pandemic, our research found a significant increase in the incidence of fetal mirror-image dextrocardia in Shaanxi Province. Most of these fetuses had mothers whose last menstrual period occurred in November 2022, within weeks 4 to 6 of COVID-19 infection. We validated our observational results by surveying the number of pregnant women with mirror-image dextrocardia in three hospitals in Shaanxi Province during three time periods: September–October 2022, November 2022, and December 2022–January 2023. The results confirmed a significantly higher incidence of mirror-image dextrocardia in fetuses whose mothers' last menstrual period occurred in November 2022, compared to those before or after this period (Figure 1).

We performed further variance analysis comparing the gestational age at which pregnant women with fetuses without fetal mirror-image dextrocardia, infected with COVID-19 during their last menstrual cycle of September–October 2022, to that of pregnant women with fetal mirror-image dextrocardia infected with COVID-19 during their last menstrual cycle of November 2022. Our findings showed 80.2% of women in the positive dextrocardia group were infected with COVID-19 during weeks 4 to 6 of pregnancy, while 93% of women in the negative dextrocardia group were infected with COVID-19 outside of weeks 4 to 6 of pregnancy. This showed a significant difference between the two groups in terms of the gestational age at infection with COVID-19.

Further analysis was performed comparing the gestational age at which pregnant women with fetuses without fetal mirror-image dextrocardia, infected with COVID-19 during their last menstrual cycle of December 2022–January 2023, with that of pregnant women with fetal mirror-image dextrocardia who were infected with COVID-19 during their last menstrual cycle of November 2022. We found 80.2% of women in the positive dextrocardia

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Table 1. Comparison of gestational weeks between pregnant women with COVID-19 infection but without fetal mirror-image dextrocardia whose last menstrual period was in September–October 2022 and pregnant women with COVID-19 infection and with fetal mirror-image dextrocardia whose last menstrual period was in November 2022

	Mirror-image dextrocardia status					
Gestational week	No	Proportion	Yes	Proportion	χ^2	P
Gestational week <4 weeks	2	2.0%	6	5.7%	128.433	<0.001
Gestational week ≥4 weeks & ≤ 6 weeks	5	5.0%	85	80.2%		
Gestational week >6 weeks	92	93.0%	15	14.1%		

Table 2. Comparison of gestational weeks between pregnant women with COVID-19 infection and fetal non-mirror-image dextrocardia whose last menstrual period was in December 2022–January 2023 and pregnant women with COVID-19 infection and fetal mirror-image dextrocardia whose last menstrual period was in November 2022

	Mirror-image dextrocardia status					
Gestational week	No	Proportion	Yes	Proportion	χ^2	P
Not pregnant during COVID-19 infection	70	68.6%	0	0	176.537	<0.001
Gestational week <4 weeks	29	28.4%	6	5.6%		
Gestational week ≥4 weeks & ≤ 6 weeks	2	2.0%	85	80.2%		
Gestational week >6 weeks	1	1.0%	15	14.2%		

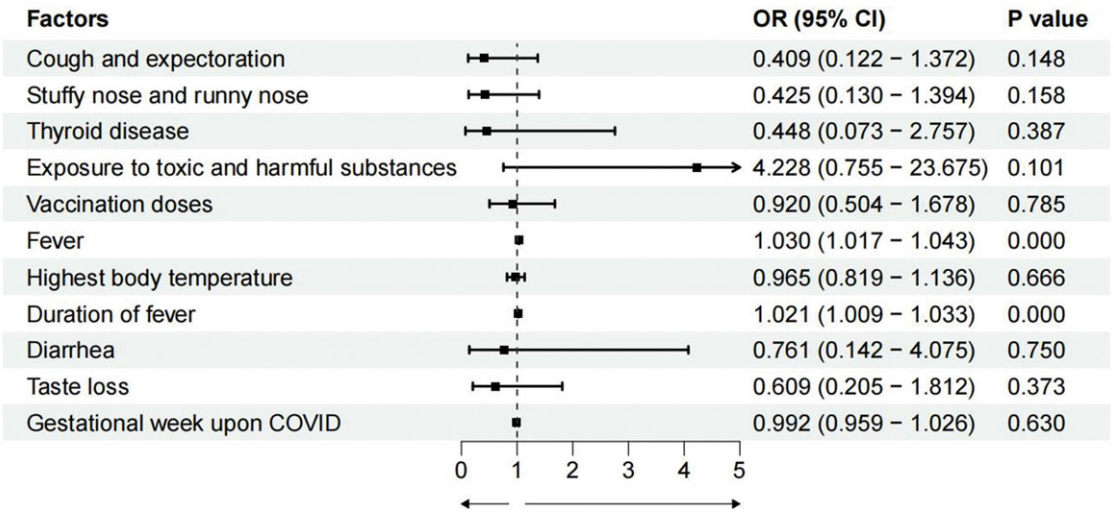

Figure 2. Create a forest map based on the results of multiple factor regression analysis.

group were infected with COVID-19 during weeks 4 to 6 of pregnancy, while 68.6% of women in the negative dextrocardia group were not pregnant at the time of infection. This showed a significant difference between the two groups in terms of the gestational age at infection with COVID-19.

Based on these findings, we suggest that COVID-19 infection during weeks 4 to 6 of pregnancy, when the heart is developing during a critical period of embryonic development, is strongly associated with mirror-image dextrocardia in fetuses. For pregnancies conceived before or after this critical period, the risk of mirror-image dextrocardia is not significantly different compared to preexisting rates.

In order to further investigate the risk factors, we searched the literature and found that less than 20% of CHDs are explained by chromosomal abnormalities and gene defects,[6,7] while most are due to the interaction of genetic and environmental factors.[8–11] Factors such as maternal viral infection during pregnancy, metabolic diseases, use of teratogenic drugs, and exposure to teratogenic substances during early pregnancy, advanced maternal age (age ≥35 years), use of assisted reproductive technology, and adverse lifestyles can increase the risk of CHD.[12,13] It is generally recognised that cold can cause fetal cardiac malformation. Cold is usually caused by virus, which replicates in cytotrophoblast cells and then enters fetal blood for infection; or it does not replicate and directly causes infection by overflowing into embryonic cells,[14] thus causing CHD in the fetus. A complex cascade of events including humoral and cell-mediated immunity occurs following exposure to SARS-CoV-2.[15] Excessive inflammation, altered immune response, cytokine storm, endothelial dysfunction, tissue hypoxia, and coagulation disorders lead to COVID-19-related

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Table 3. Single-factor analysis of pregnant women with a history of COVID-19 infection and without fetal mirror-image dextrocardia compared to pregnant women with a history of COVID-19 infection and with mirror-image dextrocardia, based on last menstrual period in November 2022

		Mirror-image dextrocardia status					
Factors	Sign	No	Proportion	Yes	Proportion	χ^2	P
Number of pregnancies	1	60	55.05%	49	44.95%	5.624	0.334
	2	27	46.55%	31	53.45%		
	3	9	34.62%	17	65.38%		
	4	4	36.36%	7	63.64%		
	5	2	50.00%	2	50.00%		
	6	1	100.00%	0	0.00%		
Number of pregnancies	0	68	53.97%	58	46.03%	4.117	0.234
	1	33	44.00%	42	56.00%		
	2	2	28.57%	5	71.43%		
	3	0	0.00%	1	100.00%		
Conception method/fertilization method	Nature assist	94	47.72%	103	52.28%	3.369	0.08
	Naturally assist	9	75.00%	3	25.00%		
Whether or not to receive vaccines	Yes	92	49.46%	94	50.54%	0.022	1.000
	No	11	47.83%	12	52.17%		
Number of vaccine doses	0	13	100.00%	0	0.00%	19.762	0.000
	1	2	28.57%	5	71.43%		
	2	25	39.06%	39	60.94%		
	3	64	91.43%	6	8.57%		
	4	0	0.00%	1	100.00%		
Fever	Yes	86	45.74%	102	54.26%	9.368	0.002
	No	17	80.95%	4	19.05%		
Highest body temperature	37.3 ~ 38°C	3	50.00%	3	50.00%	26.667	<0.001
	38.1 ~ 39°C	56	76.71%	17	23.29%		
	39.1~41°C	38	37.25%	64	62.75%		
	41°Cabove	6	21.43%	22	78.57%		
Duration of fever	$t \leq 24$	52	62.65%	31	37.35%	10.321	<0.001
	$24<t \leq 72$	48	41.38%	68	58.62%		
	t>72	3	30.00%	7	70.00%		
Gestational week during COVID-19 infection	Not pregnant during COVID-19 infection	1	100.00%	0	0.00%	3.175	0.339
	Gestational week <4 weeks	8	57.14%	6	42.86%		
	Gestational week ≥4 weeks and ≤ 6 weeks	84	49.70%	85	50.30%		
	Gestational week >6 weeks	10	40.00%	15	60.00%		
Sore throat	Yes	77	52.74%	69	47.26%	2.316	0.135
	No	26	41.27%	37	58.73%		
Diarrhea	Yes	8	27.59%	21	72.41%	6.341	0.016
	No	95	52.78%	85	47.22%		
Reduced sense of taste	Yes	31	36.05%	55	63.95%	10.242	0.002
	No	72	58.54%	51	41.46%		
Excessive sleepiness	Yes	61	50.00%	61	50.00%	0.060	0.889
	No	42	48.28%	45	51.72%		

(*Continued*)

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Table 3. (*Continued*)

Factors	Sign	Mirror-image dextrocardia status				χ^2	P
		No	Proportion	Yes	Proportion		
Weakness	Yes	84	49.41%	86	50.59%	0.006	1.000
	No	19	48.72%	20	51.28%		
Body aches	Yes	63	45.32%	76	54.68%	2.602	0.110
	No	40	57.14%	30	42.86%		
Shortness of breath and chest tightness	Yes	41	53.95%	35	46.05%	1.040	0.318
	No	62	46.62%	71	53.38%		
Cough with phlegm	Yes	61	44.20%	77	55.80%	4.193	0.043
	No	42	59.15%	29	40.85%		
Nasal congestion and runny nose	Yes	44	40.37%	65	59.63%	7.244	0.009
	No	59	59.00%	41	41.00%		
Taking medication	Yes	62	58.49%	44	41.51%	0.951	0.343
	No	67	65.05%	36	34.95%		
Diabetes mellitus	Yes	2	28.57%	5	71.43%	1.301	0.445
	No	101	50.50%	99	49.50%	1.034	0.493
Hypertension	Yes	1	100.00%	0	0.00%		
	No	102	49.04%	106	50.96%		
Hyperlipidemia	Yes	1	50.00%	1	50.00%	0.000	1.000
	No	102	49.28%	105	50.72%		
Connective tissue diseases	Yes	1	100.00%	0	0.00%	1.034	0.493
	No	102	49.04%	106	50.96%		
Thyroid diseases	Yes	3	20.00%	12	80.00%	5.544	0.029
	No	100	51.81%	93	48.19%		
Smoking	Yes	15	100.00%	0	0.00%	16.63	0.000
	No	88	45.36%	106	54.64%		
Alcohol consumption	Yes	0	0.00%	2	100.00%	1.962	0.498
	No	103	49.76%	104	50.24%		
Exposure to chemical substances	Yes	5	100.00%	0	0.00%	5.272	0.028
	No	98	48.04%	106	51.96%		
Family hereditary disease/genetic disease	Yes	3	100.00%	0	0.00%	3.132	0.118
	No	100	48.54%	106	51.46%		
Family history of visceral transposition	Yes	2	100.00%	0	0.00%	2.078	0.242
	No	101	48.79%	106	51.21%		
Exposure to pets	Yes	2	18.18%	9	81.82%	4.493	0.059
	No	101	51.01%	97	48.99%		
Exposure to harmful substances	Yes	22	81.48%	5	18.52%	12.861	0.000
	No	81	44.51%	101	55.49%		
Exposure to adverse environment	Yes	2	100.00%	0	0.00%	2.078	0.242
	No	101	48.79%	106	51.21%		

complications.[16] Tanacan et al reported that the degree of inflammation may be assessed by using complete blood cell parameters and indices. The utility of neutrophil-to-lymphocyte ratio, neutrophilXplatelet/lymphocyte (SII), and neutrophilXmonocyte/lymphocyte (SIRI) in the prediction of adverse events was evaluated in the adult population with promising results. Therefore, virus is an important factor in CHD. Genetic factors such as single gene mutation and polygenic inheritance, as well as environmental factors, such as infection, radiation, drugs, environmental pollution, food

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Table 4. Multiple logistic regression analysis was then performed on the independent risk factors obtained from the single-factor analysis, revealing that the highest body temperature during pregnancy and the duration of fever were significant risk factors for COVID-19-infected pregnant women developing fetal mirror-image dextrocardia

Factors	*B*	*SE*	*Wald*χ^2	*p*-Value	*OR*	*95%CI*
Cough and expectoration	−0.893	0.617	2.096	0.148	0.409	0.122–1.372
Stuffy nose and runny nose	−0.856	0.606	1.992	0.158	0.425	0.130–1.394
Thyroid disease	−0.802	0.927	0.749	0.387	0.448	0.073–2.757
Exposure to toxic and harmful substances	1.442	0.879	2.691	0.101	4.228	0.755–23.675
Vaccination doses	−0.084	0.307	0.075	0.785	0.920	0.504–1.678
Fever	0.029	0.007	20.285	0.000	1.030	1.017–1.043
Highest body temperature	−0.036	0.084	0.186	0.666	0.965	0.819–1.136
Duration of fever	0.021	0.006	12.149	0.000	1.021	1.009–1.033
Diarrhea	−0.273	0.856	0.101	0.750	0.761	0.142–4.075
Taste loss	−0.496	0.556	0.794	0.373	0.609	0.205–1.812
Gestational week upon COVID	−0.008	0.017	0.232	0.630	0.992	0.959–1.026
Constant	26.761	4899.652	0.000	0.996	418914992845.668	

safety, pesticides, and chemical plants, are all risk factors for CHD.[17] Şahan YÖ et al reported that maternal COVID-19 seems to have both morphological and functional effects on the fetal, neonatal, and infant heart.[18]

To further explore risk factors for mirror-image dextrocardia, we conducted a single-factor and multi-factor logistic regression analysis through an online survey on pregnant women with a last menstrual cycle in November 2022, who had a history of COVID-19 infection, but without mirror-image dextrocardia, and pregnant women with a history of COVID-19 infection and with mirror-image dextrocardia. Our results showed that there was a statistically significant difference in the incidence of fever and duration of fever between the two groups. The main reason for the difference in outcomes between the two groups of pregnant women infected with COVID-19 was the duration of fever. Women who with fetal mirror-image dextrocardia with a fever duration of more than 3 days accounted for 70.00%, while those who without fetal mirror-image dextrocardia group accounted for 30.00%. Furthermore, other symptoms of COVID-19 infection, such as sore throat, diarrhoea, cough, and expectoration, were more common in the right atrial appendage group than in the non-right atrial appendage group (Table 3). Therefore, we believe that the main reasons for the different outcomes between the two groups were the duration of fever and the severity of virus infection.

Conclusions

This study suggests that there are two key factors leading to an increase in the incidence of mirror-image dextrocardia in fetuses due to COVID-19 infection: the infection occurs during the critical period of embryonic heart development between weeks 4 and 6 during early pregnancy, and the presence of fever and a longer duration of fever.

Highlights. (1) A significant difference was noted in the gestational age at COVID-19 infection women with a September to October 2022 and December 2022 to January 2023 final menstrual period who did not bear a fetus with mirror-image dextrocardia, and those with a November 2022 final menstrual period whose fetus exhibited this condition.

(2) The univariate and multivariate analyses conducted on pregnant women with a final menstrual period in November 2022 who had contracted COVID-19 revealed significant differences in the presence and duration of fever between those bearing fetuses with mirror-image dextrocardia and those without

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Ethical standard. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the local ethical committee (IRB) (Code: 202314).

Informed consent. Informed consent was obtained from all individual participants included in the study.

Consent for publication. Not applicable.

References

1. KocA, Anaesthesia recommendations for situs inversus totalis. (2020), Available: https://www.orpha.net/data/patho/Ans/en/Situs-inversus-totalis.pdf.
2. Yilmaz S, Demirtas A, Tokpinar A, Niyazi A. Dextrocardia and situs inversus totalis in a turkish subject: a case report. Int J Morphol 2019; 37: 900–902.
3. Boon M, Smits A, Cuppens H et al. Primary ciliary dyskinesia: critical evaluation of clinical symptoms and diagnosis in pa- tients with normal and abnormal ultrastructure. Orphanet J Rare Dis 2014; 9: 11.
4. Werner C, Lablans M, Ataian M et al. An international registry for primary ciliary dyskinesia. Eur Respir J 2016; 47: 849.
5. Ajayi N, Lazarus L, Satyapal KS. Penetrating chest injury in a case of situs inversus totalis. IJAE 2019, 124: 58–64.
6. Zhu Y, Chen Y, Feng Y, Yu D, Mo X. Association between maternal body mass index and congenital heart defects in infants: a meta-analysis. Congenit Heart Dis 2018; 13: 271–281.
7. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. Lancet 2010; 375: 649–656.
8. Zhao QM, Ma XJ, Ge XL, et al. Neonatal congenital heart disease screening group. Pulse oximetry with clinical assessment to screen for congenital

heart disease in neonates in China: a prospective study. Lancet 2014; 384: 747–754.
9. Guzik TJ, Mohiddin SA, Dimarco A. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020; 116: 1666–1687.
10. European Society of Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. Accessed 17 Jun 2020.
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the chinese center for disease control and prevention. JAMA 2020; 323: 1239–1242.
12. Gelb BD, Chung WK. Complex genetics and the etiology of human congenital heart disease. Csh Perspect Med. 2014; 4: a013953. doi: 10.1101/cshperspect.a013953.
13. Liu S, Liu J, Tang J, Ji J, Chen J, Liu C. Environmental risk factors for congenital heart disease in the Shandong peninsula, China: a hospital-based case-control study. J Epidemiol 2009; 19: 122–130.
14. Tania M, Amitoz M, Paul V, Cheryl H-G, Heather LB. Prevalence of congenital cardiovascular malformations varies by race and ethnicity. Int J Cardiol 2010; 143: 317–322.
15. Silva MJA, Ribeiro LR, Lima KVB, Lima L. Adaptive immunity to SARS-coV-2 infection: a systematic review. Front Immunol 2022; 13: 1001198.
16. Priya SP, Sunil PM, Varma S, Brigi C, et al. Direct, indirect, post-infection damages induced by coronavirus in the human body: an overview. Virus 2022; 33: 1–16.
17. Tanacan A, Oluklu D, Laleli Koc B, et al. The utility of systemic immune-inflammation index and systemic immune-response index in the prediction of adverse outcomes in pregnant women with coronavirus disease 2019: analysis of 2649 cases. J Obstet Gynaecol Res 2023; 49: 912–919. doi: 10.1111/jog.15533 Epub 2022 Dec 29. PMID: 36582132
18. Şahan YÖ., Sakcak B, Göncü Ayhan Ş. et al. The influence of maternal COVID-19 on cardiac functions: from fetal life to infancy. Echocardiography 2024; 41: e15736. DOI: 10.1111/echo.15736.

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