

Original Article

Pattern of Congenital Heart Disease In Neonates Conceived In The COVID-19 Era: Single Neonatal Intensive Care Unit Experience

Eman Shafik Shafie*, Fatma Al Zahraa Mostafa, Amal El-Sisi, Amira Esmat El-Tantawy, Sara Yehia, Samira Abdelmonem

Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt; fatmaalzahraah@hotmail.com; amiraesmat@yahoo.com, amal.elsisi@kasralainy.edu.eg, sarahyehia22@gmail.com, samira_abdelmonem@yahoo.com

* Correspondence: eman_shafik84@cu.edu.eg

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Abstract:

Background: Frequency of congenital heart disease (CHD) association with Coronavirus disease 2019 (COVID-19) is lacking.

Aim of work: to study difference of frequency and pattern of congenital heart diseases among neonates conceived during the pre-COVID-19 era, and those conceived during the COVID-19 era who were admitted to the Neonatal Intensive Care Unit (NICU), Faculty of Medicine Pediatric Hospitals, Cairo University.

Material and Methods: This was a retrospective descriptive study in which we revised the files of all neonates admitted to NICU in a period of 6 months from September 2019 till February 2020 (group 1) and from September 2021 till February 2022 (group 2) who were conceived before and during the COVID era respectively.

Results: 162 newborns with CHD were enrolled in this study from a total of 1488 admitted in NICU during the 12 months of the study. 74 CHD patients were conceived in the pre COVID era (group 1) whereas 88 patients were conceived during COVID era (group 2). In group 1: 43 cases were males (58.1%) and 31 were females (41.9%), compared to group 2: where 53 were males (60.2%) and 35 were females (39.8%) ($p = 0.785$). There was no difference in frequency or type of CHD among the 2 groups. The most common CHD was patent ductus arteriosus (PDA) with and without pulmonary hypertension in 34 cases (45.9%), followed by atrial septal defect (ASD) in 19 (25.7%), then ventricular septal defect (VSD) in 7 (9.5%), which was not different than in group 2, the most common CHD was PDA with and without pulmonary hypertension in 52 cases (59.1%) then VSD in 8 (9.1%), VSD and ASD in 8 (9.1%) ($p = 0.555$).

Conclusion: The frequency and type of CHD among neonates admitted to our NICU was not different in the era before and the COVID-19 era. PDA with and without pulmonary hypertension was the commonest CHD in both eras.

Level of Evidence of Study: IV (1).

Keywords: Congenital heart disease; COVID-19; neonates.

Abbreviations: AS: aortic stenosis; ASD: atrial septal defect; AVSD: atrioventricular septal defect; CHD: congenital heart disease; COA: coarctation of aorta; COVID-19: Coronavirus disease 2019; DORV: double outlet right ventricle; NICU: Neonatal Intensive Care Units; PDA: patent ductus arteriosus; PCR: polymerase chain reaction; RDS: respiratory distress syndrome; SARS-CoV: severe acute respiratory syndrome-associated coronavirus; TGA: Transposition of great arteries; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect.

Introduction

The coronavirus disease in 2019 (COVID-19) caused serious pregnancy complications including miscarriage and fetal development restriction. Congenital abnormalities associated with COVID-19 and or the vaccine are a matter of concern (2). The suggested forms of fetal affection by COVID-19 are numerous. Angiotensin-converting enzyme 2 (ACE2) and S protein protease receptors, which are present in early-stage of human embryo development, are required for the virus to enter the cell (gametes, zygotes, and 4-cell embryos) according to a theory that attempts to explain the mechanism of SARS-CoV-2 transmission from mother to fetus in early



pregnancy, the virus has the ability to enter fetal cells at an early stage of development and alter cell transformation and growth (3). The vertical transmission of COVID-19 from the mother to the fetus was reported to be rare. Severe acute respiratory syndrome-associated coronavirus (SARS-CoV-2) was detected in the placenta of a stillborn fetus, and the connective tissue of the umbilical cord showed signs of inflammation; demonstrating transmission of the virus from mothers to their fetuses (4). IgM antibodies cannot penetrate the placenta, hence newborns born to a woman infected with SARS-CoV-2 exhibited greater IgM antibody and cytokine levels two hours after birth, suggesting in utero viral infection (5).

One of the first organs to develop and start functioning during the embryonic stage is the human heart. The four chambered heart is fully created by week 7 of pregnancy. Heart genesis defects result during the embryonic development of the heart (6). It is not clear if COVID-19 may play a role in the development of congenital heart defects so it is important to look into the effects of SARS-CoV-2 infection on fetuses at an early stage of pregnancy in order to handle any fetal defects that may arise and reduce neonatal morbidity and mortality (7). It might be related to SARS-CoV-2 due to infection or to the induced immune vasculopathy, that compromises oxygen delivery and organogenesis (8). We aimed to compare frequency and pattern of congenital heart disease (CHD) among neonates conceived during the pre-COVID-19 era, and those conceived during the COVID-19 era who were admitted to the Neonatal Intensive Care Unit (NICU), Faculty of Medicine Pediatric Hospitals, Cairo University.

Subjects and Methods

This was a retrospective descriptive study conducted at NICU, Faculty of Medicine Pediatric Hospitals, Cairo University to determine the pattern of CHD in neonates conceived in the pre COVID era who were admitted to NICU during a period of 6 months from September 2019 till February 2020 (group 1). The pattern of CHD was compared to those conceived during the COVID era and admitted to NICU from September 2021 till February 2022. The study was approved by the Research Ethics Committee, Faculty of Medicine, Cairo University, Egypt (MS-575-2021). Written informed consent from mother of each patient was obtained after proper orientation regarding the objectives of the study. Data confidentiality and informants' identity were maintained throughout the study and were coded and accessed by the investigators only.

Participants

We revised the files of all neonates admitted to NICU of Pediatric Hospital, Cairo University in the designated periods mentioned earlier. The study included files of all preterm and full-term neonates with confirmed CHD by echocardiography (using General Electric vivid 5 Echo machine, USA). Data relevant to history of maternal exposure to or infection by COVID 19, were collected and compared to type of CHD. The study dates were chosen to compare those who were conceived before and during the pandemic.

Statistical Analysis

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables for comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Results

The total number of patients admitted in NICU during 6 months in pre and 6 months in post COVID era were 1488. During the pre-COVID-19 era from September 2019 till February 2020 the total number of admission of neonates in NICU was 716 with 74 cases having CHD (group 1), while during the COVID era from September 2021 till February 2022, the total number of admission of neonates in NICU was 772 with 88 cases having CHD (group 2). (Figure 1). Total admissions were not different in the 2 eras ($p=0.555$). There was no difference among the 2 groups as regard the gestational age and the gender. In group 1: 34 neonates were born full term (45.9%) and 40 (54.1%) were preterm, while in group 2: 31 neonates (35.2%) were full term and



57 (64.8%) were preterm (p = 0.166). In group 1: 43 were males (58.1%) and 31 were females (41.9%), while in group 2: 53 were males (60.2%) and 35 were females (39.8%) (p = 0.785).

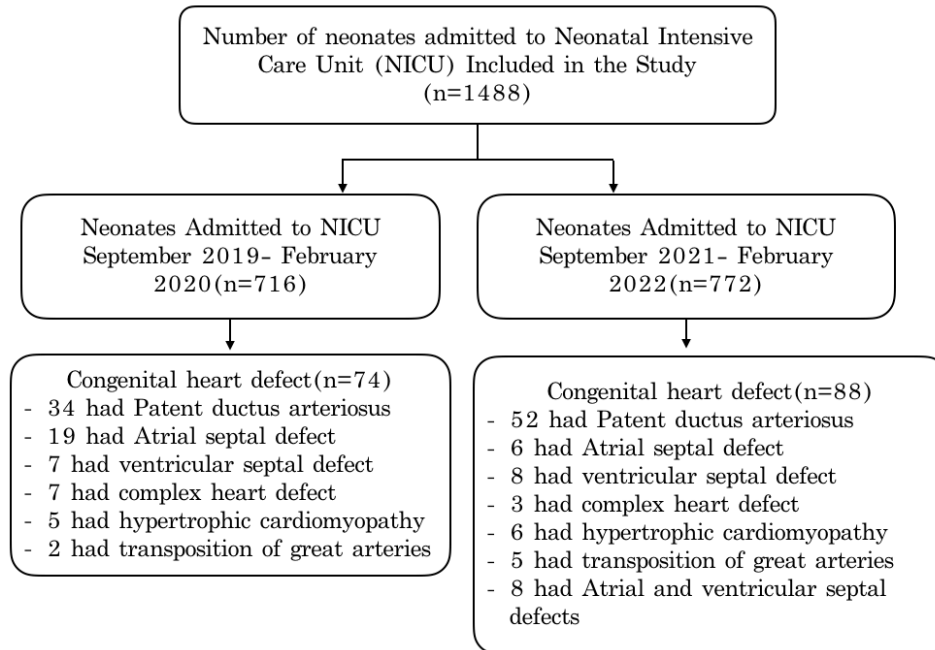


Figure 1. flow chart of studied neonates.

Among the 162 neonate with CHD, the commonest clinical presentation of CHD was cyanosis in 12 (7.2%) neonates in both groups and by examination it was the presence of a cardiac murmur in 43 (26%) neonates. (Table 1). Echocardiography revealed preponderance of PDA with and without pulmonary hypertension. (Table 2).

Table 1. The clinical presentations of the studied groups

	Group 1 Conceived in Pre- COVID-19 era N=74		Group 2 Conceived in Post- COVID-19 era N=88		P value
	Number	%	Number	%	
Cyanosis	6	8.1	6	6.8	0.755
Edema	3	4.1	9	10.2	0.135
Tender Liver	0	0.0	1	1.1	1
Murmur	15	20.3	28	31.8	0.097
Cardiomegaly	5	6.8	7	8.0	0.772

Table 2. Echocardiographic finding of studied groups

	Group 1 Conceived in Pre- COVID-19 era Number =74		Group 2 Conceived in Post- COVID-19 era Number =88		P value
	Number	%	Number	%	
PDA with and without pulmonary hypertension	34	45.9	52	59.1	0.8
ASD	19	25.7	6	6.8	
VSD	7	9.5	8	9.1	
Complex heart disease	7	9.5	3	3.4	
Hypertrophic cardiomyopathy	5	6.8	6	6.8	
TGA	2	2.7	5	5.7	
VSD and ASD	0	0.0	8	9.1	

ASD: Atrial septal defect; PDA: Patent ductus arteriosus; TGA: Transposition of great arteries; VSD: Ventricular septal defect.



Among group 2; 69 (78.4%) had positive history of maternal illness in the form of fever, cough, diarrhea, of them 46 mothers (52.3%) tested positive for COVID by COVID polymerase chain reaction test during pregnancy, while another 42 mothers (47.7%) had history of household contacts with symptoms suspecting COVID or tested positive for COVID. The most common symptom suggestive of COVID infection in the mothers was cough (36 cases) followed by fever (25 cases) then diarrhea (8 cases). The first trimester was found to be the most common at which symptoms appeared with a total number of 37 cases (42%). (Table 3).

Table 3. Maternal COVID 19 infection among those conceived during COVID-19 era.

Maternal history		Neonates born during COVID 19 pandemic			
		N=88		%	
Cough		36		40.9	
Fever		25		28.4	
Diarrhea		8		9.1	
Trimester at which symptoms appeared	1st	37		42	
	2nd	21		23.9	
	3rd	30		34.1	
		Positive PCR test for COVID 19			
		Yes		No	
		Number	%	Number	%
Trimester at which mothers tested positive	1st	19	21.6	18	20.5
	2nd	14	15.9	7	8
	3rd	13	14.7	17	19.3
		Household contacts with symptoms suspecting COVID or positive for COVID (Maternal history)			
		Yes		No	
		Number	%	Number	%
Trimester	1st	18	20.5	19	21.6
	2nd	7	8	14	15.9
	3rd	17	19.3	13	14.7

COVID-19: Coronavirus disease 2019; PCR: polymerase chain reaction.

Discussion

The fear of COVID-19 induction of CHD among neonates is justifiable. During the pandemic the COVID-19 morbidity was reported to reach 30.2% (9), hence if COVID-19 was capable of induction of CHD in general or induces a specific type of CHD during the embryogenesis, we would expect an increase in the number of neonates with CHD. CHD among the neonates is a diagnostic and management challenging burden. The teratogenic effect of SARS was suspected to result from the virus or the related medications as ribavirin (10). The placental viremia detected by PCR in the third trimester of a newborn neonate with neurological compromise raised suspicion, but was disputed as a cause. The placental changes were related to vascular thromboses, malformations and villitis, but was not shown to be associated with teratogenicity (11). The fetal thrombotic vasculopathy of placenta is a well-known pathological entity, not limited to COVID-19. It is associated with maternal diabetes mellitus, maternal autoimmune disease, maternal thrombophilia or to cord lesions, viral infections, etc. It results in still birth, cerebral palsy, brain infarcts and hypoxic ischemic encephalopathy. (12)

Congenital COVID-19 was reported to be silent or cause respiratory distress, and in less than 3% cause severe pneumonia (13). It was also reported to cause miscarriage, preterm labor, and fetal demise (14). The teratogenic effect is not proved but considered a possibility.

Our study failed to find a difference in frequency or type of CHD among neonates conceived before or during the COVID-19 era who admitted to NICU. Our study is a pilot study, that is supported by the work of Birth Defect Research Study in United states, that clearly reported that the COVID-19 infection during the earliest 12 weeks of organogenesis in pregnancy was not associated with higher incidence of teratogenicity (15).

The small sample size in our study precludes solid evidence against the cardiac teratogenicity of COVID-19. It is not a prevalence or incidence study. The COVID-19 pandemic cost lives, exhausted massive financial resources and huge social burden, but its scope of effect on newborns seems to be related to the vasculopathy, more than to a direct teratogenic effect.



Conclusion

The frequency and type of CHD among neonates admitted to our NICU was not different in the era before and the COVID-19 era. PDA with and without pulmonary hypertension was the commonest CHD in both eras.

Author Contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sara Yehia, Eman Shafik Shafie and Samira Abdelmonem. The first draft of the manuscript was written by Fatma Alzahraa Mostafa, Eman Shafik and Amira Esmat EL Tantawy and all authors critically appraised the initial drafts of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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