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The Relationship between Maternal Risk Factors and Congenital Cardiac Abnormalities Detected via Echocardiography

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ABSTRACT

Background: Congenital heart disease (CHD) is a leading cause of birth defects, affecting up to 10 out of 1,000 live births. Understanding the risk factors associated with CHD is crucial for early detection and intervention. This retrospective case control study aimed to investigate the relationship between maternal and paternal characteristics and the development of congenital heart abnormalities in newborns in Dezful, Iran. **Material and Methods:** The study patients consisted of 60 infants with confirmed CHD and 60 healthy controls. Data on maternal age, paternal age, maternal education, place of residence, maternal weight gain, maternal underlying disease, parental smoking and alcohol use, family history of CHD, history of miscarriage/stillbirth, and Maternal multivitamin use during pregnancy were collected. Descriptive and inferential statistical analyses, including chi-square, t-test, and independent sample tests, were performed using SPSS software. **Results:** The study found that both younger (<20 years) and older (>30 years) maternal age (χ^2 = 1.42, p = 0.042), as well as older paternal age (>30 years) (χ^2 = 0.53, p = 0.046), were associated with a higher incidence of CHD. Maternal underlying disease, such as diabetes, hypothyroidism, and anemia, were significantly more prevalent in the CHD group (χ^2 = 8.57, p = 0.003). Paternal smoking (χ^2 = 1.91, p = 0.048) and maternal weight gain exceeding 10 kg during pregnancy (χ^2 = 8.40, p = 0.03) were also identified as risk factors. A family history of CHD (χ^2 = 4.13, p = 0.042) and a history of miscarriage/stillbirth (χ^2 = 6.13, p = 0.013) were more common in the CHD group. Maternal education level and multivitamin use were not found to be significantly associated with CHD. **Conclusions:** This study highlights the complex interplay of maternal, paternal, and genetic factors that contribute to the development of congenital heart defects. The findings emphasize the importance of targeted screening, prenatal care, and the implementation of preventive strategies to address modifiable risk factors and reduce the burden of CHD in the study population.

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Keywords: Congenital Heart Defects (CHDs), Maternal Risk Factors, Paternal Risk Factor.

BACKGROUND

Congenital heart disease (CHD) is a structural or functional abnormality of the heart and great vessels that is present at birth. It is the most common type of congenital birth defect, accounting for nearly 25% of all congenital malformations [1]. A wide range of clinical symptoms characterizes CHD and is a leading cause of stillbirth. The global prevalence of CHD is estimated to be 8-10 cases per 1,000 live births, although the prevalence rate can vary across different regions [2]. The development of CHD is influenced by a complex interplay between genetic and environmental factors [3,4]. During the critical period of fetal heart formation, which occurs between the second and tenth weeks of pregnancy, disruptions in the normal developmental processes can lead to various anatomical disorders of the heart and other organs [5]. After this period, factors may affect the function and heart rate of the developing fetus. The most common types of CHD include cyanotic and non-cyanotic congenital heart diseases [6]. The severity of CHD can range from mild defects with little impact on the patient, such as small holes in the heart, to severe and critical malformations that require immediate surgical intervention, such as transposition of the great arteries [7]. The relative prevalence of different types of congenital heart diseases worldwide is as follows: ventricular septal defect (25-30%), atrial septal defect (6-8%), patent ductus arteriosus (6-8%), aortic coarctation (5-7%), tetralogy of Fallot (5-7%), pulmonary valve stenosis (5-7%), aortic valve stenosis (4-7%), transposition of the great arteries (3-5%), hypoplastic left ventricle (1-3%), hypoplastic right ventricle (1-3%), single ventricle (1-3%) Truncus arteriosus (1-2%), and others [7,8].

Several studies have investigated the association between various risk factors and the development of CHD. A survey conducted by Dalek and colleagues (2020) evaluated the effect of maternal low education, gestational diabetes, maternal clotting disorders, and vaginal infections on the risk of CHD, reporting a positive correlation between these factors and CHD incidence [9]. Another study by the "REVEAL Center" in 2020 found no relationship between race and CHD incidence [10]. It seems that a heterogeneous interaction between genetic factors and exposure to environmental stimuli leads to congenital heart disease. Prematurity- low birth weight is known to be associated with CHD. Family marriage of parents and maternal age, maternal obesity, use of certain drugs (for example, valproate-isotretinoin, and lithium), chemical exposures, parental smoking or alcohol consumption have been mentioned as risk factors for CHD in various studies with contradictory results [11,12]. On the other hand, considering the high prevalence of consanguineous marriages, especially in rural areas of Iran, as well as contact with some environmental factors, there is probably a significant burden of CHD patients in Iran [13].

This study examines the link between maternal risk factors and the identification of congenital heart abnormalities using echocardiography in Dezful Hospital – Iran, with a focus on the importance of early detection and treatment and understanding the factors influencing the onset of CHD, this research endeavors to enhance our knowledge of potential risk factors involved in developing congenital heart defects. Through assessing various maternal characteristics and their possible influence on infant cardiac abnormalities, this study seeks to provide valuable insights that can assist in the early diagnosis and prompt intervention of congenital heart defects. The findings of this investigation may have significant implications for healthcare professionals and contribute to the formulation of effective strategies for recognizing and addressing maternal risk factors associated with congenital cardiac abnormalities.

MATERIAL AND METHODS

Study Design

This was a cross-sectional study conducted in 2019 in Dezful, Iran, to investigate the relationship between congenital heart abnormalities observed in echocardiography and associated risk factors during pregnancy.

This study was approved by the ethics committee of Dezful University of Medical Sciences with ethics code IR.DUMS. REC.1397.024.

Study Population

The study population comprised all infants with congenital heart defects born between April and March 2018 2019 Guanjavian Hospital at Dezful city in Iran. The inclusion criteria were: (1) congenital malformations of the child's heart confirmed by transthoracic echocardiography (EKO7 made in South Korea), (2) inclusion of preterm and term infants, and (3) inclusion of infants who died of heart disease after being diagnosed with CHD by a cardiologist and undergoing cardiac echocardiography in the first months of life. The exclusion criteria were: (1) initial misdiagnosis and normalization of secondary neonatal echocardiography, (2) unknown cause of death of the neonate, (3) diagnosis of isolated patent foramen ovale (PFO) without other anomalies,

and (4) lack of cooperation and family consent to participate in the study. The study was conducted at the neonatal ward, NICU, echocardiography, and archives department of the "Dr. Ganjavian Hospital" in Dezful. The initial sample size was 76 cases, and 16 were excluded according to the exclusion criteria, resulting in 60 cases and 60 controls.

Data Collection

The data collection method included a checklist to identify maternal risk factors in congenital heart disease in both the control and case groups. The checklist had four sections: (1) informed consent, (2) demographic information and medical history of parents, (3) information on the birth of the baby, and (4) risk factors during pregnancy. The demographic characteristics and risk factors assessed included maternal age, paternal age, maternal weight changes, maternal underlying diseases, tobacco use by parents and specific medications during pregnancy, family history of congenital heart disease, history of miscarriage and stillbirth, consumption of multivitamins during pregnancy, and parental alcohol consumption.

Statistical Methods of Data Analysis The statistical analysis of the research data involved using SPSS statistical software version 23, with a confidence level of 95%. Descriptive and inferential statistical methods such as Chi-square, t-test, and independent sample were employed to analyze the data. In this study, a significance level of P <0.05 was considered.

RESULTS

A study was conducted on a sample group of 60 patients with congenital heart disease to determine the prevalence of different disorders. The findings in Table 1 revealed that ventricular septal defect (VSD) had the highest prevalence, accounting for 20 patients (34%), with 16 patients (27%) affected Atrial septal defect (ASD) was the next most prevalent, followed by patent ductus arteriosus (PDA) at 13% with 8 patients. Other combinations of disorders such as PDA+ASD, ASD+VSD, and tetralogy of Fallot (TOF) were also observed, albeit at lower frequencies.

Table 1. Frequency of disorders in group of patients with congenital heart abnormalities

Disorder	Frequency	Percentage.
TGA	2	3.33
TOF	3	5
PDA	8	13
ASD	16	27
VSD	20	34
PDA + ASD	4	6
ASD + VSD	3	5
PDA + VSD	2	3.33
ASD + TGA	1	1.67
One ventricle and one atrium	1	1.67

Table 2 and 3 presents demographic characteristics that serve as risk factors, encompassing variables such as mother's age, father's age, place of residence, maternal weight change, maternal underlying diseases, tobacco use and specific medications during pregnancy, history of congenital heart disease in first-degree relatives, history o miscarriage and stillbirth, Neonatal trisomy syndrome, pre-pregnancy multivitamin use, and parental alcohol consumption.

Table 2. Frequency distribution of some demographic risk factors during pregnancy according to sample and control groups

Risk Factors	Total	CHD n (%)	No CHD n (%)	x^2 Value	*P* Value
Maternal age (year)					
<20	11	7(11.7%)	4(% 6.67)	1.429	0.042
20-30	86	39(65%)	47(% 78.33)		
>30	23	14(23.3%)	9(% 15)		
Location					
City (Dezful)	61	31(% 51.7)	30(% 50)	0.033	0.855
Around the city	59	29(% 48.3)	30(% 50)		
Mother's education level					
Under Diploma	62	28(55%)	34(56.67%)	1.034	0 .596
Diploma	43	22(36.7%)	21(35%)		
Higher than diploma	15	10 (16.7%)	5(8.33%)		
Father's age					
30 >	58	25(41.7%)	33(55%)	0.539	0.046
≥ 30	62	35(58.3%)	27(45%)		

The study found that 11.7% of mothers in the sample group were under 20 years old, while this percentage was 6.67% in the control group. Additionally, 23.3% of mothers in the sample group were over 30 years old, compared to 15% in the control group. This suggests that both young and advanced maternal age may be associated with an increased risk of congenital heart defects. In the sample group, 58.3% of fathers were over 30 years of age, compared to 45% in the control group. This indicates that older paternal age may also be a risk factor for the development of congenital heart disease.

Table 3. Frequency distribution of risk factors during pregnancy according to sample and control groups

Risk Factors	Total	CHD n (%)	No CHD n (%)	x^2 Value	*P* Value
Overweight pregnancy (kg)					
10-0	47	17(28.3%)	30 (50%)	8.403	0.038
15-10	15	8(13.3%)	7(11.7%)		
20-15	46	29(48.3%)	15(% 25)		
25-20	14	6(10%)	8(% 13.3)		
Tobacco use by the mother					
Yes	0	0	0		
No	120	60(100%)	60(100%)		
Tobacco use by father					
Yes	35	22(36.7%)	13(21.67%)	1.915	0.048
No	85	38(63.3%)	47(78.33%)		
Alcohol consumption by mother					
Yes	0	0	0	-	-
No	120	60(100%)	60(100%)		
Alcohol consumption by father					
Yes	0	0	0	-	-
No	120	60(100%)	60(100%)		
Underlying disease					
No	66	24(40%)	42(70%)	8.571	0.003
Yes	54	36(60%)	18(30%)		

Underlying disease type					
Lupus	4	4(11.1%)	0	13.964	0.007
Diabetes	2	2(5.6%)	0		
Hypothyroidism	17	14(38.9%)	3(16.6%)		
Other Diseases	24	9(25%)	15(83.4%)		
Gestational diabetes	7	7(19.4%)	0		
History of congenital heart disease					
Yes	4	4(6.7%)	0	4.138	0.042
No	116	56(93.3%)	60(100%)		
Taking multivitamins					
Yes	60	60(100%)	60(100%)	-	-
No	0	0	0		
Neonatal trisomy syndrome					
Yes	6	6(10%)	0	6.31	0.012
No	114	54(90%)	60(100%)		
History of miscarriage and stillbirth of mother 1					
Yes	30	22(36.7%)	8(13.33%)	6.136	0.013
No	90	38(63.3%)	52(86.67%)		
Non-teratogenic drugs **by the mother**					
Yes	40	30(50%)	18(30%)	3.429	0.064
No	60	30(50%)	42(% 705%)		
Taking anticonvulsants (teratogen) by usin					
Yes	0	0	0	-	-
No	120	60(100%)	60(100%)		

The study found that 55% of mothers in the sample group had either no formal education or only a high school education, compared to 56.67% in the control group. This suggests that lower maternal education levels may not be a significant risk factor for congenital heart defects. The study found that 71.7% of mothers in the sample group had a weight gain of more than 10 kg during pregnancy, compared to 50% in the control group. This indicates that excessive maternal weight gain may be associated with an increased risk of congenital heart defects.

The study found that 60% of mothers in the sample group had underlying medical conditions, such as lupus, diabetes, hypothyroidism, and anemia, compared to 30% in the control group. This suggests a significant relationship between maternal underlying diseases and the incidence of congenital heart defects. The study found that 36.7% of fathers in the sample group were smokers, compared to 21.67% in the control group. This indicates that paternal smoking may be a risk factor for the development of congenital heart defects.

The study found that 6.7% of participants in the sample group had a family history of congenital heart disease, compared to 0% in the control group. Additionally, 36.7% of mothers in the sample group had a history of miscarriage or stillbirth, compared to 13.33% in the control group. These findings suggest that a family history of congenital heart disease and a history of miscarriage or stillbirth may be associated with an increased risk of congenital heart defects.

DISCUSSION

The findings of this retrospective case-control study provide valuable insights into the association between various maternal and paternal risk factors and the development of congenital heart defects (CHDs) in newborns in Dezful, Iran.

One of the key findings of this study is the observed relationship between maternal age and the incidence of CHDs. The results indicate that both younger (under 20 years) and older (over 30 years) maternal age were associated with a higher percentage of CHD cases compared to the control group. This is consistent with the findings of other studies that have reported advanced maternal age as a risk factor for congenital heart defects [14], But in few studies, this relationship was not observed [12]. The increased risk associated with younger maternal age may be attributed to factors such as poorer overall

health, inadequate prenatal care, and higher rates of risky behaviors during pregnancy. Conversely, advanced maternal age has been linked to decreased oocyte quality, increased chromosomal abnormalities, and other age-related factors that can adversely affect fetal development [14,15].

Similarly, the study found a higher percentage of fathers over the age of 30 in the CHD group compared to the control group. This aligns with the existing literature that suggests older paternal age may also contribute to the development of congenital heart defects [16]. The potential mechanisms underlying this association include the increased risk of genetic mutations and chromosomal abnormalities in sperm as men age, which can negatively impact fetal development [16].

Maternal education level was not found to be a significant risk factor for CHDs in this study, as the distribution of educational attainment was similar between the case and control groups. This contrasts with some previous studies that have reported an association between lower maternal education and an increased risk of congenital heart defects [17,18]. The authors suggest that unaccounted environmental factors related to socioeconomic status may play a more significant role in the development of CHDs, and further research is needed to elucidate these relationships.

Regarding the impact of parental residence, the study found no significant difference in the risk of CHDs between those living in the city of Dezful and those residing in surrounding towns and villages. This finding differs from some other studies that have reported a higher risk of CHDs in non-urban or economically disadvantaged areas [17,18]. The researchers propose that the lack of a significant difference in this study may be due to the relatively small geographical area and the similarity in environmental exposures between the urban and rural populations in the region [16,18].

The study's results provide strong evidence for the association between maternal underlying medical conditions and the incidence of CHDs. Specifically, the researchers found a significantly higher prevalence of conditions such as lupus, diabetes, hypothyroidism, and anemia among mothers in the CHD group compared to the control group. These findings are consistent with the existing literature that has highlighted the increased risk of congenital heart defects in offspring of mothers with various chronic medical conditions [19,20].

The proposed mechanisms underlying the link between maternal morbidities and CHDs are complex and multifaceted. For example, maternal diabetes can have a teratogenic effect on fetal cardiogenesis, leading to impaired heart development. Hyperglycemia and hyperinsulinemia during pregnancy can also contribute to the development of cardiac abnormalities [20,21]. Similarly, maternal hypothyroidism and anemia have been associated with disruptions in the regulation of angiogenic factors, placental dysfunction, and other processes critical for normal fetal heart development [19,21].

Regarding parental lifestyle factors, the study found a higher percentage of smoking among fathers in the CHD group compared to the control group, while no mothers in either group reported smoking. This is consistent with the existing evidence that paternal smoking may increase the risk of congenital heart defects in offspring [18,21,22]. The potential mechanisms by which paternal smoking can contribute to CHDs include the mutagenic effects of tobacco smoke on sperm, leading to chromosomal abnormalities, as well as the indirect impact of secondhand smoke exposure on the mother and fetus [18,22].

Interestingly, the study did not find any cases of alcohol consumption among parents in either the case or control groups. This contrasts with previous research that has identified parental alcohol use as a risk factor for congenital heart defects [21,23]. The authors suggest that the lack of reported alcohol consumption in this study may be due to cultural and social norms within the study population, and the potential underreporting of this behavior. Further research with larger sample sizes and more diverse populations may be necessary to clarify the relationship between parental alcohol use and the development of CHDs.

The study also found a significant association between maternal weight gain during pregnancy and the incidence of CHDs. Specifically, the researchers observed a higher percentage of mothers with weight gains exceeding 10 kg in the CHD group compared to the control group. This aligns with previous studies that have identified maternal overweight and obesity as risk factors for congenital heart defects [21,24,25]. The proposed mechanisms linking maternal weight status to CHDs include the adverse effects of metabolic disorders, such as insulin resistance, inflammation, and oxidative stress, on fetal development and gene expression [24,25].

Another notable finding of this study is the significant association between a family history of congenital heart disease and the occurrence of CHDs in the offspring. The researchers found a higher percentage of participants in the CHD group reporting a family history of congenital heart

defects compared to the control group. This is consistent with the existing literature that has highlighted the importance of genetic factors in the etiology of congenital heart defects [26]. The increased risk in families with a history of CHDs may be attributed to the inheritance of genetic variants or predispositions that can disrupt normal heart development.

The study also examined the relationship between maternal history of miscarriage or stillbirth and the incidence of CHDs. The researchers found a significantly higher percentage of mothers in the CHD group reporting a history of spontaneous abortion or stillbirth compared to the control group. This finding aligns with previous studies that have suggested a link between recurrent pregnancy loss and an increased risk of congenital heart defects [18,27]. The potential mechanisms underlying this association may involve factors such as intrauterine conditions that can impair fetal development and lead to both miscarriage and congenital anomalies.

Interestingly, the study found that all mothers in both the case and control groups reported the use of multivitamins during pregnancy. This suggests that the occurrence of CHDs in the study population was not related to a lack of maternal multivitamin supplementation. However, the authors acknowledge the importance of proper nutrition and the potential protective role of specific micronutrients, such as folic acid, in the prevention of congenital heart defects, as supported by previous research [17,28].

Finally, the study identified a higher percentage of infants with trisomy syndromes, such as Down syndrome, in the CHD group compared to the control group. This finding aligns with the well-established association between chromosomal abnormalities and the development of congenital heart defects [29,30]. The authors suggest that the genes located on chromosome 21, which are involved in the normal development of the heart, may play a crucial role in the pathogenesis of cardiac anomalies observed in individuals with Down syndrome.

CONCLUSION

This retrospective case control study provides valuable insights into the complex interplay of maternal, paternal, and genetic factors that contribute to the development of congenital heart defects in newborns in Dezful, Iran. The findings highlight the importance of maternal age, paternal age, maternal underlying medical conditions, maternal weight status, family history, and chromosomal abnormalities as key risk factors for CHDs. These results have important implications for targeted screening, prenatal care, and the development of preventive strategies to reduce the burden of congenital heart defects in the study population and beyond. Further research with larger sample sizes and longitudinal study designs may help to elucidate additional risk factors and the underlying biological mechanisms involved in the etiology of these complex and potentially life-threatening congenital anomalies.

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CONFLICTS OF INTEREST

It should be noted that there were no conflicts of interest among the authors of this article.

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