http://www.cjmb.org

doi 10.34172/cjmb.2022.26

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 9, No. 3, July 2022, 153–160
eISSN 2148-9696

The Predisposing Risk Factors for Non-syndromic Congenital Heart Disease: A Case-Control Study

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Abstract

Objectives: Despite the importance of congenital heart disease (CHD) in the population, the risk factors predisposing infants to be born with non-syndromic CHD are not well understood yet.

Materials and Methods: In a case-control study, we recruited consecutive 109 infants with non-syndromic CHD who were referred to our pediatric cardiac care clinic and then compared them with 117 infants without CHD (2015-2016). Paternal, maternal, and neonatal demographic information, maternal past medical history, and antenatal history were recorded for each child. To investigate the potential risk factors for developing CHD, infants with and without CHD were compared in terms of study variables. In a second analysis, preterm infants were excluded and term infants were compared regarding the study variables.

Results: The findings revealed that higher maternal and paternal education were both associated with a lower risk of CHD (odds ratio [OR]: 0.47, 95% confidence interval [CI]: 0.24-0.93, $P=0.031$, and OR: 0.45, 95% CI: 0.23-0.89, $P=0.023$, respectively). The family history of CHD in the first- or second-degree relatives of infants was significantly associated with CHD (OR: 3.56, 95% CI: 1.35-9.40, $P=0.007$). Several parameters were more prevalent in the CHD group, including having lower birth weight, having preterm birth, being the fourth birth order or higher, and not receiving maternity care under the supervision of a gynecologist. However, higher birth order and lower birth weight were not associated with CHD in exclusively term infants. Finally, a higher maternal educational level was related to lower CHD in term infants even after adjusting for a family history of CHD and preconception diabetes mellitus (OR: 5.45, 95% CI: 1.71-17.37, $P=0.004$).

Conclusions: Our study findings demonstrate the need for a more enhanced primary care program, especially in patients with poor financial status and a family history of CHD.

Keywords: Congenital heart disease, Risk factors, Age, Antenatal history

Introduction

The prevalence of congenital heart disease (CHD), which constitutes nearly one-third of major congenital abnormalities, has been considerably increasing in recent years (1-3). Although the mean birth prevalence of CHD varies in different geographical areas, it is estimated to be 8.2 for every 1000 live-birth globally (3). The incidence of CHD was reported to be 3.3 per 1000 births in Iran and this further differs in various regions of the country (4). CHD imposes a great health burden on world societies although the risk factors predisposing infants to be born with CHD are not well recognized yet.

Although there is a complex genetic basis for CHD, not all affected individuals have recognized genetic abnormality (5). Further, it is estimated that among some CHD subtypes, about 30% of cases can be associated with some identifiable possible risk factors (6). Various maternal and paternal prenatal exposures and diseases, as well as different pregnancy-related risk factors, have been linked to the increased number of infants born with CHD. However, the results of different studies are not consistent and conclusive (7-14). On the other hand, there is a paucity of information regarding influential factors on the incidence of CHD in Iran as a developing country. Accordingly, understanding the predisposing factors for CHD helps physicians in better management of higher-risk pregnancies and public health services for planning more effective interventions.

Regarding these facts, this case-control study from the north-west of Iran aimed to investigate the association of parents' demographic factors and maternal diseases during pregnancy and neonatal history at birth with the presence of non-syndromic CHD diagnosed after birth or during the infancy period.

Materials and Methods

Study Population and Protocol

In this case-control study, we recruited infants with a final diagnosis of CHD and compared them with healthy infants regarding study variables from March 2015 to March 2016. The case group consisted of all infants who were referred to our tertiary level pediatric cardiac

Received 16 April 2020, **Accepted** 27 August 2020, **Available online** 19 March 2021

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Key Messages

What is the current knowledge?

- CHD constitutes approximately one-third of all major congenital anomalies and is considered a major global health burden.
- Despite its importance and increasing prevalence in recent years, the underlying predisposing factor for the development of CHD is unknown in many non-syndromic CHDs.
- Recent studies have suggested various risk factors for CHD although the results of different studies are inconclusive and the research is ongoing in this area.

What is the innovation of this study?

- Maternal and paternal ages are not associated with non-syndromic CHD risk in both univariate and multivariate analyses.
- The family history of CHD in the first- and second-degree relatives of infants is an independent predictor of CHD in infants.
- Although lower birth weight and higher birth order are more prevalent in the CHD group, these factors are not associated with CHD after excluding preterm infants.
- Higher maternal education is a protective factor for CHD in infants in both univariate and multivariate analyses.

care clinic in Tabriz, which is the major referral center in the north-west of Iran, and found to have CHD. The presence of CHD was confirmed in all cases based on the echocardiographic examination. During one year, all cases were prospectively enrolled in this study. For each identified case, a control case was randomly selected on the same day among the otherwise healthy infants who were presented to the general pediatric clinic of our hospital for the evaluation of acute respiratory infections. Adopted infants and infants with genetic syndromes based on genetic and clinical evaluations were all excluded from this study. The parents of nine CHD cases did not agree with the inclusion of their infants in this study. Finally, our case group consisted of 109 CHD infants and the control group included 117 healthy infants.

One trained physician interviewed the mothers of cases and controls and filled out prepared questionnaires based on interview information and medical documentation. Paternal, maternal, and neonatal demographic information, maternal past medical history, and antenatal history were recorded for each child. The study variables included maternal and paternal age at conception, maternal and paternal educational levels, presence of CHD in the infant's mother or father or their first- or second-degree relatives, maternal smoking before conception, and preconception maternal diabetes type 1 or type 2. Moreover, other parameters were gestational diabetes, history of hypertension, history of anemia before pregnancy or in the first trimester, maternal fever in the first trimester, gender and birth order of the infant, birth weight, and the mother's total number of live births, stillbirths, and miscarriages. Additionally, planning a pregnancy, being an assisted pregnancy, getting the first maternity care in the first eight weeks of gestation, having the first positive pregnancy test in the first eight weeks of gestation, and having maternity care under the supervision of a gynecologist, along with the delivery type and preterm birth were other included variables. The mothers were also asked about their pre-pregnancy experiences regarding their perceived support from the husband, the paternal family, and the maternal family, as well as general life satisfaction, and financial problems before pregnancy. They were also questioned about their satisfaction with their pregnancy.

To investigate the potential risk factors for developing CHD, children with and without CHD were compared regarding the study variables. Although all eligible infants were included in this study regardless of their prematurity status, a second analysis for comparing cases and controls was planned in our study protocol to be exclusively performed in term infants. Based on previously published data, in which preconception diabetes (10) and family history of CHD (15) were among the most suspected risk factors for CHD, we planned to also report the association of study variables with CHD after adjustment for these two variables.

Statistical Analysis

Data were analyzed with the software program IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp). Categorical and continuous variables were presented as frequencies and percentages as well as mean ± standard deviation, respectively. Moreover, Categorical and continuous variables were compared using the chi-square test or Fisher's exact test and independent *t* test, respectively. Multivariate logistic regression analysis was used to adjust study variables for the confounding effects of preconception diabetes and family history of CHD in term infants, as described previously. Crude and adjusted odds ratios with a 95% confidence interval were stated, and a two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Table 1 presents the maternal history of children with and without CHD. The mean maternal age at the beginning of pregnancy was not statistically different between infants with and without CHD (28.06 ± 6.67 vs. 28.09 ± 5.11 years, $P = 0.971$). Similarly, the mean paternal age at the beginning of pregnancy was similar in infants with and without CHD (32.38 ± 6.70 vs. 32.81 ± 5.70 years, $P = 0.601$). Maternal and paternal educational levels (i.e., college-level degree vs. school-level education) were significantly associated with CHD. In addition14.7% of mothers of the CHD group and 26.7% of mothers of the non-CHD group had a college level or a higher educational level (OR: 0.47, 95% CI: 0.24-0.93, $P = 0.031$). Based on the results, 14.7% and 27.4% of fathers of the CHD and non-CHD groups had

Table 1. The Association of Parenteral and Neonatal Risk Factors and CHD in the Entire Study Sample

	No CHD	CHD	Odds Ratio	*P* Value
Maternal age	28.09±5.11	28.06±6.67	0.99 (0.95-1.04)	0.971
Maternal age groups				0.113
<20	6 (5.1%)	6 (5.5%)	Reference	
20-24	22 (18.8%)	28 (25.7%)	1.27 (0.36-4.49)	
25-29	43 (36.8%)	37 (33.9%)	0.86 (0.25-2.89)	
30-34	31 (26.5%)	17 (15.6%)	0.54 (0.15-1.96)	
35+	15 (12.8%)	21 (19.3%)	1.40 (0.37-5.19)	
Paternal age	32.81±5.70	32.38±6.70	0.98 (0.94-1.03)	0.590
Paternal age groups				0.353
<20	0 (0.0%)	1 (0.9%)	-	
20-24	5 (4.3%)	8 (7.3%)	Reference	
25-29	33 (28.2%)	31 (28.4%)	0.58 (0.17-1.98)	
30-34	35 (29.9%)	39 (35.8%)	(0.20-2.32)	
35+	44 (37.6%)	30 (27.5%)	0.42 (0.12-1.42)	
Maternal education (Collage degree or higher)	31 (26.5%)	16 (14.7%)	0.47 (0.24-0.93)	0.031
Paternal education (Collage degree or higher)	32 (27.4%)	16 (14.7%)	0.45 (0.23-0.89)	s0.023
Family history of CHD	6 (5.9%)	18 (18.4%)	3.65 (1.39-9.60)	0.007*
Maternal smoking	2 (1.7%)	4 (3.7%)	2.19 (0.39-12.2)	0.432
Diabetes before or during pregnancy	8 (7.5%)	11 (10.9%)	0.66 (0.25-1.71)	0.473
Preconception type 2 diabetes	4 (3.4%)	11 (10.1%)	3.17 (0.97-10.22)	0.054
Gestational diabetes (Excluding pregestational diabetes)	4 (3.5%)	0 (0%)	-	-
Preconception hypertension or diagnosed in the first trimester	30 (25.6%)	26 (23.9%)	0.95 (0.69-1.31)	0.761
Anemia	22 (20.4%)	26 (26.0%)	1.37 (0.71-2.62)	0.411
Fever in the first trimester	6 (6.1%)	3 (3.2%)	0.50 (0.12-2.08)	0.498
Gender of neonate (male %)	72 (61.5%)	73 (67.0%)	0.78 (0.45-1.36)	0.395
Preterm birth	6 (5.1%)	28 (25.7%)	1.95 (1.55-2.45)	<0.001*
Birth weight (g)	3044±537	2846±756	1.01 (1.00-1.02)	0.025
Birth order				0.030*
First born	49 (41.9%)	46 (42.2%)	Reference	
Second born	47 (40.2%)	32 (29.4%)	0.72 (0.39-1.32)	
Third born	14 (15.7%)	17 (16.3%)	1.06 (0.49-2.29)	
Fourth born or higher	2 (2.2%)	12 (11.5%)	4.61 (1.23-17.25)	
Unintended pregnancy	19 (17.1%)	26 (24.5%)	1.57 (0.81-3.05)	0.185
Assisted pregnancy	2 (1.8%)	0 (0.0%)	-	-
Number of children	1.90.82±	1.70.88±	0.94 (0.59-1.49)	0.281
History of still births	2 (1.7%)	5 (4.6%)	0.66 (0.40-1.08)	0.267
History of miscarriages	14 (12.0%)	18 (16.5%)	0.46 (0.14-1.55)	0.430
First maternity care in the first 8 weeks of gestation	104 (93.7%)	95 (92.2%)	0.79 (0.27-2.28)	0.676
First positive pregnancy test in first 8 weeks of gestation	104 (93.7%)	95 (92.2%)	1.13 (0.41-3.15)	0.791
Maternity care under the supervision of gynecologist	87 (74.4%)	64 (58.7%)	0.49 (0.27-0.86)	0.013*
Cesarean section	77 (67.5%)	72 (66.1%)	0.93 (0.53-1.63)	0.887

Note. CHD: Congenital heart diseases.

a college level or higher educational level (OR: 0.45, 95% CI: 0.23-0.89, $P=0.023$), respectively. Infants with CHD were significantly more likely to have a family history of CHD compared to those without CHD (18.4% vs. 5.9%, OR: 3.56, 95% CI: 1.35-9.40, $P=0.007$). The prevalence of maternal smoking was 3.7% and 1.7% in the CHD group and the other group with no significant difference, respectively ($P=0.432$). The results further revealed that preconception maternal diabetes mellitus (DM) was present in 10.1% of the CHD group in comparison to the 3.4% of the non-CHD group (OR: 3.17, 95% CI: 0.97-10.22, $P=0.054$). All mothers with preconception diabetes had type 2 DM. Gestational diabetes was only present in four mothers of the control group. The maternal history of preconception hypertension, CHD, anemia, and fever in the first trimester of pregnancy were similar in groups with and those without CHD (Table1).

The mean number of previous miscarriages and stillbirths of mothers was statistically similar in groups with and without CHD (Table1). The prevalence of unintended pregnancy was 24.5% vs. 17.1% in infants with and without CHD with no significant difference ($P=0.185$). Based on the findings, 11.4% of mothers of the CHD group rated their life satisfaction as poor in comparison to 13.2% of mothers of the non-CHD group ($P=0.837$). The rate of the self-reported poor financial

status of the family was significantly higher in the CHD group compared to the non-CHD group (23.1% vs. 11.2%, $P=0.020$). As shown in Table 1, the mean neonatal birth weight was significantly lower in the CHD group in comparison to the non-CHD group (2864.17 ± 756.45 vs. 3044.75 ± 537.14 grams, $P=0.028$). There was no gender difference between the two groups ($P=0.374$). Of the CHD group, 65.2% were males and 56.4% of the group without CHD were males. The prevalence of mothers, given birth with cesarean section, was similar in the two groups. In the CHD group, prenatal care was less likely to be under the direct supervision of a gynecologist in comparison to the non-CHD group (58.7% vs. 74.4%, $P=0.013$).

Table 2 provides the comparison of the CHD and non-CHD groups after excluding preterm deliveries. Higher maternal and paternal education levels were both associated with a lower likelihood of CHD. A family history of CHD was also more common in the CHD group. Maternity care under the direct supervision of a gynecologist was less common in the CHD group as well.

After adjustment for the confounding effects of the family history of CHD and maternal preconception DM, higher maternal education was significantly associated with lower CHD (Table3).

Table 4 summarizes the comparison of the two groups regarding their pre-pregnancy experiences regarding

Table 2. The Association of Parenteral and Neonatal Risk Factors and CHD in the Study Sample After Excluding Infants With Preterm Births

	No CHD (n=111)	CHD (n=81)	Odds Ratio (95% CI	*P* Value
Maternal age	28.04±5.01	28.24±6.64	1.01 (0.95-1.05)	0.811
Maternal age groups				0.193
<20	5 (4.5%)	4 (4.9%)	Reference	
20 to 24	22 (19.8%)	20 (24.7%)	1.13 (0.26-4.83)	
25 - 29	42 (37.8%)	30 (37.0%)	0.89 (0.22-3.60)	
30-34	29 (26.1%)	11 (13.6%)	0.47 (0.10-2.09)	
35+	13 (11.7%)	16 (19.8%)	1.53 (0.34-6.92)	
Paternal age	32.75±5.62	32.25±5.85	0.98 (0.93-1.03)	0.552
Paternal age groups				0.153
<20	0 (0.0%)	0 (0.0%)	-	
20-24	4 (3.6%)	6 (7.4%)	Reference	
25-29	32 (28.8%)	20 (24.7%)	0.41 (0.10-1.66)	
30-34	35 (31.5%)	35 (43.2%)	0.66 (0.17-2.57)	
35+	40 (36.0%)	20 (24.7%)	0.33 (0.08-1.32)	
Maternal education (Collage degree or higher)	31 (27.9%)	12 (14.8%)	0.45 (0.21.94)	**0.034**
Paternal education (Collage degree or higher)	32 (28.8%)	13 (16.0%)	0.47 (0.22-0.97)	**0.041**
Family history of CHD	4 (4.2%)	14 (19.2%)	5.39 (1.69-17.19)	**0.004**
Maternal smoking before conception	2 (1.8%)	2 (2.5%)	1.38 (0.19-10.06)	0.750
Diabetes before or during pregnancy	8 (7.8%)	8 (11.0%)	1.44 (0.51-4.05)	0.483
Preconception type 2 diabetes	4 (3.6%)	8 (9.9%)	2.93 (0.85-10.09)	**0.088**
Gestational diabetes (Excluding pregestational diabetes)	4 (3.7%)	0(0.0%)	-	-
Hypertension before pregnancy or in first trimester	28 (25.2%)	22 (27.2%)	1.05 (0.73-1.53)	0.892
Anemia	19 (18.6%)	20 (26.7%)	1.58 (0.77-3.24)	0.204
CHD in mother	1 (1.1%)	2 (2.8%)	2.49 (0.22-28.06)	0.460
Fever in the first trimester	6 (6.5%)	1 (1.4%)	0.204 (0.024-1.73)	0.146
Gender of neonate (male)	69 (62.2%)	56 (69.1%)	1.36 (0.74-2.50)	0.317
Birth weight of infant (grams)	3102.3±465.9	3063.8±619.8	1.00 (0.99-1.00)	0.629
Birth order				0.222
First pregnancy	47 (42.3%)	33 (40.7%)	Reference	
Second pregnancy	44 (39.6%)	25 (30.9%)	0.80 (0.41-1.57)	
Third pregnancy	17 (15.3%)	16 (19.8%)	1.34 (0.59-3.03)	
Forth pregnancy or higher	3 (2.7%)	7 (8.6%)	3.32 (0.80-13.8)	
Number of live births	1.93±0.83	1.77±0.83	0.78 (0.52-1.16)	0.634
History of still births	1 (0.9%)	3 (3.7%)	0.55 (0.30-0.99)	0.312
History of miscarriages	13 (11.7%)	12 (14.8%)	0.86 (0.55-1.34)	0.679
Unintended pregnancy	18 (17.0%)	21 (26.6%)	1.77 (0.86-3.60)	0.116
Assisted pregnancy	2 (1.9%)	0 (0.0%)	-	-
First maternity care in the first 8 Weeks of gestation	7 (6.6%)	5 (6.6%)	0.99 (0.30-3.26)	0.990
First positive pregnancy test in the first 8 weeks of gestation	7 (6.4%)	4 (5.3%)	0.82 (0.23-2.90)	0.761
Maternity care under the supervision of a gynecologist	81 (73.0%)	48 (59.3%)	0.53 (0.29-0.99)	**0.047**
Cesarean section	73 (67.6%)	56 (69.1%)	0.93 (0.51-1.73)	0.822

Note. CHD: Congenital heart diseases.

Table 3. Adjusted Odds Ratios With a 95% CI for Study Variables in Term Infants

	Adjusted Odds Ratio (95% CI)	*P* Value
Maternal age	0.98 (0.93-1.04)	0.620
Paternal age	0.96 (0.91-1.01)	0.170
Maternal education (Collage degree or higher)	0.45 (0.21-0.98)	0.045
Paternal education (Collage degree or higher)	0.54 (0.24-1.05)	0.071
Family history of CHD[a]	5.45 (1.71-17.37)	0.004
Maternal smoking before conception	1.72 (0.20-17.62)	0.699
Diabetes before or during pregnancy[b]	1.42 (0.49-4.11)	0.516
Preconception type 2 diabetes[b]	2.77 (0.78-9.84)	0.115
Gestational diabetes (Excluding pregestational diabetes)	--	
Hypertension before pregnancy or in first trimester	0.97 (0.50-1.96)	0.992
Anemia	0.67 (0.32-1.39)	0.671
Fever in the first trimester	1.81 (0.01-1.73)	0.138
Gender of neonate (male)	1.65 (0.86-3.17)	0.127
Birth weight of infant (grams)	1.00 (0.99-1.01)	0.336
Birth order		
First pregnancy	Reference	0,321
Second pregnancy	0.74 (0.37-1.47)	0.397
Third pregnancy	1.06 (0.44-2.56)	0.881
Forth pregnancy or higher	2.91 (0.66-12.69)	0.155
Number of live births	0.67 (0.44-1.03)	0.074
History of still births	3.92 (0.37-40.98)	0.294
History of miscarriages	1.33 (0.55-3.17)	0.517
Unintended pregnancy	1.68 (0.80-3.51)	0.168
Assisted pregnancy	-	
First maternity care in the first 8 weeks of gestation	0.953 (0.281-3.236)	0.938
First positive pregnancy test in the first 8 weeks of gestation	0.768 (0.204-2.89)	0.696
Maternity care under the supervision of gynecologist	0.558 (0.297-1.049)	0.070
Cesarean section	1.10 (0.58-2.10)	0.761

Note. CI: Confidence interval; CHD: Congenital heart diseases. Odds ratios are adjusted for the family history of congenital heart defects and preconception maternal diabetes mellitus.

[a] Adjusted only for maternal preconception diabetes.

[b] Adjusted only for a family history of congenial heart defects.

social and financial stressors in the whole study sample and after the exclusion of preterm infants. Finally, the mothers of infants with CHD were more likely to report poor emotional support from the paternal family and having financial problems before pregnancy.

Discussion

Our results revealed that higher maternal education, higher paternal education, family history of CHD in the first- or second-degree relatives of infants, lower birth weight, preterm birth, being the fourth birth order or higher were more prevalent in infants with CHD in comparison to the control group. The mothers of infants with CHD were less likely to receive maternity care under the supervision of a gynecologist. There was a non-significant trend toward higher preconception DM in mothers of the CHD group. However, our results demonstrated that higher birth order and lower birth weight were not associated with CHD after the exclusion of preterm infants from both cases and controls.

Different genetic factors can lead to the development of CHD, including chromosomal abnormalities, subchromosomal deletions, or duplications and single-gene mutations. However, no genetic component could be identified in the majority of CHD patients (16), leading to investigations for identifying the environmental factors that predispose the fetus to develop CHD. However, the exact mechanisms by which various possible environmental factors exert their effect on the normal development of the cardiovascular system is still uncertain. Although some CHD subtypes appear soon after birth or during the infancy period, some mild cases remain undetected, making the investigations more challenging for finding the possible causes (17).

Although the role of genetics has been emphasized in the literature, the exact genetic components of non-syndromic CHD need further investigation and approval (18). Our study points to the association of CHD with a family history of CHD, which provides additional clinical evidence for the genetic components of CHD. In a study by Snijder et al, maternal but not paternal family history of CHD was associated with CHD (12). Likewise, Chou et al found maternal CHD as a predisposing factor for CHD in the offspring (19). Given that our findings show a strong association between the family history of CHD and the risk of development of CHD even after adjustment for

Table 4. Comparison of the CHD Group With the Control Group Regarding Social and Financial Stressors

	No CHD	CHD	Odds Ratio	*P* value
Perceived poor support from the husband	3 (2.6%)	5 (4.6%)	0.85 (0.39-1.82)	0.490
Perceived poor support from the paternal family	10 (8.7%)	25 (23.4%)	3.20 (1.45-7.04)	0.003
Perceived poor support from the maternal family	6 (5.5%)	11 (10.3%)	0.96 (0.47-1.96)	0.214
Poor maternal satisfaction for being pregnant	16 (13.8%)	10 (9.5%)	0.65 (0.28-1.52)	0.325
Poor financial status	12 (11.2%)	25 (23.1%)	2.38 (1.12-5.04)	0.020
Poor life satisfaction of the mother	15 (13.2%)	12 (11.4%)		0.837
After excluding preterm infants				
Perceived poor support from the husband	2 (1.9%)	3 (3.8%)	2.06 (0.33-12.65)	0.433
Perceived poor support from the paternal family	9 (8.3%)	19 (23.8%)	3.46 (1.47-8.13)	0.004
Perceived poor support from the maternal family	5 (4.8%)	8 (10.1%)	2.06 (0.33-12.65)	0.433
Poor maternal satisfaction for being pregnant	15 (13.6%)	7 (9.0%)	1.60 (0.62-4.13)	0.454
Poor financial status	10 (9.9%)	18 (22.5%)	2.64 (1.14-6.10)	0.034
Poor life satisfaction of the mother	13 (12.0%)	9 (11.4%)	0.94 (0.38-2.32)	0.893

Note. CHD: Congenital heart diseases.

preconception diabetes in term infant, a careful assessment of the familial history of CHD in preconception and prenatal care is of great importance.

Regarding the association of CHD with maternal and paternal age, there are conflicting results in the literature (20-22). In the current study, no association was found regarding maternal or paternal age with the risk of CHD in infants even after adjustment for family history of CHD and DM after excluding preterm infants., Schofield et al also reported no significant association between maternal age and CHD risk (23). Similarly, Best et al demonstrated no relationship between maternal age at delivery time and CHD (7). Likewise, Fung et al discovered no association between either maternal or paternal age with the risk of CHD without a genetic basis. Nevertheless, both factors were associated with genetic-related CHD (21). In contrast, some studies revealed an association between higher maternal age but not paternal with CHD (12, 24). Abqari et al found that both maternal and paternal ages were related to certain types of CHD in the offspring (24). In another study, Olshan et al also reported an association between age and risk of CHD among patients with ventricular septal defects, atrial septal defects, and patent ductus arteriosus (25). In an analysis of non-chromosomal birth defects, Reefhuis and Honein identified an increased risk of CHD in mothers of 35-40 years of age (20). The association of maternal age and the risk of CHD may also be affected by racial or ethnic variations (14), which may partly describe the differing results of studies in various countries. It is believed that this may necessitate complete prenatal screening programs in mothers regardless of their age.

Maternal diseases and environmental exposures before or during pregnancy may also predispose offspring to CHD (8,19,26,27). Based on our results, a non-significant trend was found toward a higher prevalence of mothers with preconception type 2 DM in the CHD group. Likewise, Oyen et al reported a higher risk for developing CHD in the offspring of mothers with type 1 or 2 DM. Their findings also revealed that the risk might further increase in mothers with an acute complication of pregestational diabetes (8).

We found no association between smoking during pregnancy and CHD. However, it should be mentioned that there were few smoker mothers in our study sample. In a meta-analysis, cigarette smoking was not found to be related to CHD risk (28) although another meta-analysis established the association of smoking with an increased risk of CHD (29).

The results of our study regarding the association of lower birth weight with CHD confirm previous findings in the literature (12,23,30). However, in our study, lower birth weight was no longer associated with CHD after excluding preterm infants from the analysis. We also found that the mothers of the CHD group were less likely to receive maternity care under the supervision of a gynecologist. Considering the suggested role of vitamin and folic acid supplementations in decreasing the risk of CHD (11, 27) and the association of a higher maternal educational level with a lower risk of CHD in our study, this finding may suggest the preventive role of more evidence-based prenatal care, delivered by a gynecologist and better compliance of mothers with the prescribed supplements. However, a better understanding of the reasons for this finding needs further investigation.

Interestingly, we found higher maternal and paternal educational levels as protective factors for CHD, and the maternal education level remained significant even after adjustment for confounding factors. In addition, self-reported economic problems in the family before conception were associated with a higher prevalence of CHD. Globally, the prevalence of CHD is shown to differ based on the income level of the countries. Although the prevalence of CHD is reported to be the lowest in the low-income countries of Africa, under-diagnosis is suggested as the cause of this finding (3,31). In line with

our findings, the results of a meta-analysis indicated the negative association of the higher maternal educational level and higher family income with the risk of CHD in the offspring (32). Access to healthcare, environmental factors and genetic composition may all contribute to the observed differences.

Conclusions

In general, the results of our study demonstrate that maternal and paternal ages are not associated with CHD in both univariate and multivariate analyses. A family history of CHD in the first- or second-degree relatives of infants is a significant predictor of CHD in infants even after adjustment for maternal preconception DM. Higher maternal education is associated with a lower risk of CHD in infants even after excluding preterm infants and adjustment for maternal preconception DM and family history of CHD. Eventually, our finding represents the need for a more enhanced primary care program, especially in patients with poor financial status and a family history of CHD regardless of the maternal and paternal age.

Limitations

This is a preliminary single-center study from a pediatric cardiology clinic with a limited number of cases. Considering that the number of patients in each CHD subtype was limited, it was impossible to analyze the risk factors for each CHD subtype. This study only focused on live infants with CHD and had no information regarding cases who had died of the disease after live birth or the CHD cases which resulted in abortion or stillbirth. We also used a case-control study by a questionnaire, which predisposes the study to recall-bias. Larger population-based studies preferably including all prenatally diagnosed CHDs are needed to investigate the suggested risk factors of our study in more detail.

Authors' Contribution

SG: concept and design; SF and MNB: data collection and interpretation of the data; NK and KGD: performing of the study and writing of the draft; MM, RN and RP: data analysis, article summary and article submission; AT: wrote the manuscript, final editing was done. All authors read and approved the study.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

The Ethics Committee of Tabriz University of Medical Sciences reviewed and approved the study protocol (the approval number of 91/9/27-5/4/8817). Informed consent for participation was obtained from the parents of the included infants. All study protocols followed the ethical standards of the research and Ethics Committee of Tabriz University of Medical Sciences and with the Helsinki Declaration of 1975, as revised in 2013. Complete patient privacy was maintained in all steps of this study.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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