Incidence and Risk Factors of Congenital Heart Disease in Qingdao: A Prospective Census Study

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Abstract

Background The incidence of congenital heart disease (CHD) were greatly inconsistent among many studies with a range from 4/1,000 to 50/1,000. A large prospective population study was performed to investigate the incidence and find risk factors of congenital heart disease (CHD) during fetal and neonatal period.

Methods A prospective cohort study was conducted in Qingdao, China, from August 1, 2018 to April 30, 2019. All local registered pregnant were continuously investigated and followed from the first trimester to delivery, collecting the characteristics of pregnant and their newborns. A Poisson regression model was applied to assess the association between CHD and possible risk factors.

Results The incidence of fetal CHD and neonatal CHD are 15.84 per 1000 fetuses and 7.32 per 1000 live births, respectively. Results from Poisson regression indicated that, countryside (0.821; 95% CI, 0.730-0.920) and first gestation (0.890; 95% CI, 0.813-0.975) was negatively associated with CHD. However, paternal factors such as multi-fetal infants (RR: 1.631, 95% confidence interval, CI: 1.276-2.036), greater than high school degree (1.390; 95% CI, 1.129-1.701), illness in 1st trimester (1.214; 95% CI, 1.080-1.359), family history of CHD (2.480; 95% CI, 1.362-3.967), and having a baby with birth defect before (1.780; 95% CI, 1.300-2.345) were positive associated with CHD.

Conclusion The incidence of CHD in Qingdao was similar to existing research. Compared with neonate, the incidence of CHD is higher in fetal. Multi-fetal infants, greater than high school degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before were correlated with an increased risk of CHD. This prospective study would provide great implications for on CHD intervention.

Introduction

Congenital heart disease (CHD) is typically defined as a structural abnormality of the heart and/or great vessels during the embryonic period, also known as congenital heart malformation.¹ Since the beginning of the 21st century, CHD has been the most frequent form of congenital anomaly in newborn infants all over the world, which accounted for one-third of all anomalies with high mortality.² Updated systematic review and meta-analysis of 260 studies revealed that between 1970 and 2017, the prevalence of CHD globally increased by 10% every 5 years.³

Until now, many studies have been conducted to assess the incidence of CHD, however, results were greatly inconsistent among these studies with a range from 4/1,000 to 50/1,000.⁴ In Japan, researchers described the prevalence of circulatory system malformations that was 3.6/1,000 births, from a prefecture-wide hospital-based birth cohort at the beginning of 12 weeks gestation.⁵ In North America, a prevalence of 6.9 per 1,000 live births (95% CI: 6.7–7.1) was reported in the CHD cases.² Recently, CHD was identified in 1103 neonates, with an updated overall prevalence of 8.98 per 1000 in 18 hospitals in China, including the eastern and western regions.⁶ In addition, it revealed that the difference of CHD

incidence in different areas may be attributed to geographical, demographic, socio-economic variations.⁷ Genetic and environmental factors are the two most important factors independently affecting the risk of CHD.⁸⁻⁹ Strikingly, more and more data revealed the different incidences of CHD in different areas. We think that the main reason why these incidences of CHD were different maybe attributed to study methods, just as sampling monitor, which could make bias obtaining the inaccurate data. However, in order to assess the accurate incidence of CHD, we conducted a municipal census and prospective cohort study, involving all the pregnant women in Qingdao.

To our best knowledge, this has been the first study evaluating the incidence of CHD and detecting associated risk factors through a census and prospective cohort study. Additionally, we achieved a full time tracking for CHD, from the first trimester to the neonatal stage. This prospective study would improve the knowledge of CHD in China, and provide great implications for CHD intervention.

Methods

Study design and data collection

Data collection

The prospective census-based cohort was defined as a birth cohort enrolling all registered pregnant women (15-20 weeks of gestation) during August 1, 2018 and April 30, 2019 in Qingdao. All these registered pregnant women were observed continuously from the first trimester to newborn, to track the fetus and newborn CHD cases. The study is carried out by Qingdao Municipal Center for Birth Defect Control and Prevention (QMCBDPC), and Qingdao Women and Children's Hospital (QWCH). We used the dataset of the cohort from August 1, 2018 to April 30, 2019, enrolling 64763 registered pregnant women in 15-20 weeks of gestation. Pregnant women use their ID number as the unique identification number linking information in different stages of gestation. Antenatal care is provided by the maternal and child health care system. This system includes 64 delivery hospitals, 65 prenatal screening blood collection hospitals, 10 district-level women and children's health centers and a municipal women and children's health care center (Qingdao Women and Children's Hospital). Qingdao Women and Children's Hospital is the coordination institution of the Women and Children's Health Care System. The 65 prenatal screening blood collection hospitals are the antenatal care providers (Down's screening-a test for prenatal detection of Trisomy 21 (Down's syndrome)) for pregnant women. This system includes detailed information about all pregnant women in Qingdao until their delivery.

Definitions

In our study, we identified all CHD cases from fetus to birth. All fetal CHD cases are diagnosed by fetal ultrasound scan, and neonatal CHD cases are diagnosed by echocardiography, cardiac catheterization and magnetic resonance angiography (MRA) in need.¹⁰⁻¹² Prenatal cardiac ultrasound allows identification of most types of congenital heart disease in second trimester.¹² The screening of perinatal infants for CHD is conducted by the obstetric and pediatric professionals. Generally, Pulse oximetry

screening,¹³ clinical observation, physical examination and echocardiography detect are the main methods to confirm CHD in newborns, but auxiliary examinations such as X-ray, electrocardiography, are applied when necessary. A fractional (as opposed to functional) oxygen saturation of $\geq 94\%$ was accepted as normal.¹⁴⁻¹⁶ A suspected case is defined as any newborns with SpO₂ (Saturation) $< 94\%$ in room air or visible cyanosis, abnormal fetal echocardiography, unexplained congestive heart failure, murmur, abnormal ECG, abnormal heart sounds, abnormal blood pressure, differential peripheral pulses, and abnormal chest x-ray. The accuracy of our screening method has been proven to be satisfactory.¹⁷ Isolated interatrial shunt (including secundum atrial septal defects and patent foramen ovale), patent ductus arteriosus among fetal and neonates < 28 days of life were excluded because they are normal fetal and neonatal findings. This study was approved by the Ethics Commission of Qingdao Women and Children's Hospital (QFFLL-KY-2020-11) and written informed consent was obtained from involved patients prior to enrollment. To minimize bias among hospitals, investigators and echocardiographers, we provide systematic training for the staffs committed to the survey.

Data statistical analysis

Continuous and categorical variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR) where appropriate. In order to detect the independent factors of CHD, the univariate and multivariate analysis were performed. Mann-Whitney U test, Chi-square test or Fisher's exact test were first conducted with a total of 16 factors between CHD and no CHD groups. Poisson regression model was then performed with significant factors selected by univariate analysis to test out the independent factors for CHD. The association between independent factors and CHD was quantified by relative risk (RR). Meanwhile, sensitivity analysis was conducted to guarantee robust results through logistic analysis. A p value less than 0.05 (two-tailed) was considered statistically significant. Analysis was performed using R software (version 3.6.2).

Results

Characteristics of included population

Of the total of 64,763 pregnant with 15-20 weeks of gestation at the time of entry into the cohort, we were able to identify 805 (1.24%) pregnant with termination of pregnancy, abortion or stillbirth, and 63,844 (99.82%) of pregnant delivering newborns. Outcome from 114 (0.18%) of pregnant were missing in the neonatal stage. The median age of pregnant was 30.62 years old (IQR:28-33), the median age of partner was 31.59 years old (IQR:28-35). Detailed characteristic information and significant P value of factors was represented in Table 1.

Outcome

Among all pregnant, 1,026 were identified as abnormal fetal echocardiogram, and a fetal CHD incidence was calculated as 15.84 per 1000 fetuses. 114 of them chose to terminate their pregnancy due to fetal CHD, and 912 of them delivered the newborns. Of the 912 delivered newborns, there were 426 live births

diagnosed as CHD, and 372 were diagnosed as CHD, followed by 114 without data of outcome. Moreover, of the 63,958 live births, 468 newborns were diagnosed as CHD, including 426 cases identified in fetal stage and 42 cases only identified in birth. The neonatal CHD incidence was 7.32 per 1000 live births. The detailed outcome information from fetal to neonatal stages was shown in Figure 1.

Among all the CHD cases, including fetuses and newborns, the incidence of CHD was classified by ICD-11. As shown in Table 2, the CHD cases were classified to thirty categories, based on separately groups of fetuses, terminations and newborns. The predominant types of CHD in fetal stage were congenital tricuspid regurgitation (29.43%), ventricular septal defect (26.71%), multiple structural developmental anomaly of heart or great vessels (8.19%), and vascular ring (7.50%). In neonatal stage, the predominant types of CHD were ventricular septal defect (34.40%), congenital tricuspid regurgitation (18.80%), multiple structural developmental anomaly of heart or great vessels (13.25%), and vascular ring (11.54%). The main types of CHD in termination were multiple structural developmental anomaly of heart or great vessels (24.56%), Tetralogy of Fallot (16.67%), ventricular septal defect (10.53%) and Structural developmental anomaly of heart or great vessels, unspecified (8.77%). the incidence of the main tapes of CHD in fetal and neonatal stage are shown directly in Figure 2.

Factors associated with CHD

We evaluated the effect of each factor on CHD by Mann-Whitney U test, Chi-square test or Fisher's exact test. Fetus, BMI (Body Mass Index) and educational level of pregnant women, living location, assisted reproduction, fertility history and the number of pregnancy, any illness in 1st trimester pregnancy, history of having a child with birth defects, history of birth defect in pregnant women, family history of birth defect and CHD, folic acid intake, history of husband smoking before pregnancy were significantly related to CHD . Multivariate Poisson regression was then performed with the significant factors selected by univariate analysis. Poisson regression model was then performed with significant factors selected by univariate analysis to test out the independent factors for CHD. Figure 3 summarized the results of multivariate analysis, which showed that multi-fetal infants (RR: 1.631, 95% CI: 1.276-2.036), greater than high school degree (RR: 1.390; 95%CI: 1.129-1.701), illness in 1st trimester (RR: 1.214; 95% CI: 1.080-1.359), family history of CHD (RR 2.480; 95% CI: 1.362-3.967), and having a baby with birth defect before (RR: 1.780; 95% CI: 1.300-2.345), countryside (RR: 0.821; 95% CI: 0.730-0.920) and first gestation (RR: 0.890; 95% CI: 0.813-0.975) were independently associated with CHD, suggesting that multi-fetal infants, high school degree or college degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before would increase the risk of CHD but countryside and first gestation decreasing the risk.

Sensitivity analysis was conducted to guarantee robust results. As shown in Figure 4, the logistic regression analysis was performed to quantify the association between these significant factors detected by univariate analysis and CHD event.

Discussion

Previous studies from different area in China have reported various incidence of CHD, which ranged from 6.87 to 76.00 per 1000 children.^{5, 18–23} To our best knowledge, this has been the first time that performed a prospective census-based cohort study investigating all local pregnant and their newborns to respectively evaluate incidence and type of CHD during fetal and neonatal period, and analyze the potential risk factors, which provides new knowledge of CHD control and prevention. Our study indicates that the incidence of CHD in fetuses is twice for that in newborns. Of the 64,763 participants, 1,026 (15.84‰) had fetal congenital heart disease. Of the 63,958 live births (including 114 newborns of missing birth record), 468 (7.32‰) newborns were diagnosed CHD. The highest incidence of fetal CHD is congenital tricuspid regurgitation accounting for 29.43% (304/1,026), followed by malformations of ventricular septal defect 26.71% (274/1,026). However, the highest incidence of neonatal CHD is ventricular septal defect 34.40% (161/468), followed by congenital tricuspid regurgitation 18.8% (88/468). The type with highest incidence in our study is consist with the previous reported by Egbe A, et al.⁵ However, the type with second high incidence is different, which is atrial septal defect detected by Egbe A. For this difference, the main reason maybe that isolated patent foramen ovale and patent ductus arteriosus are excluded in our study because they are normal neonatal findings during fetal and neonatal period. Compared with previous studies, our study could evaluate more accurate incidence of CHD on the basis of conducting the prospective census-based cohort study. The higher incidence of CHD in fetuses than newborns, indicates that prenatal screening and diagnosis are significantly important for CHD control and prevention. Moreover, our findings provide some important implications for the prevention and management of CHD. First of all, abortion and stillbirth should be extremely concerned for pregnant with critical CHD fetuses. Moreover, it should be avoided that pregnant with light and mild cardiac abnormality select termination. Last but not least, even if fetuses identified as CHD, they still have a chance to become health when they are born, due to the subsequent development of tissues and organs. Overall, fetal CHD screening is very important for the early detection and intervention of CHD.

As previous studies have suggested, the variation in CHD incidence was attributed to cases of minor CHD, but severe CHD remained stable.⁴ In our report, 114 of 1,026 pregnant women with fetal CHD chose to terminate their pregnancy. CHD classified as simple, moderate, complex. Among these terminated cases, sample CHD cases, moderate and complex CHD accounted for 24.56% (28/114 fetuses), 17.54% (20/114 fetuses), 49.12% (56/114 fetuses) respectively. 10 of 114 terminated cases were cardiac abnormal but not identify the type of fetal CHD. Meanwhile, the vast majority of fetuses with congenital tricuspid regurgitation are more likely to repair itself when they are born, as well as about half of fetuses with ventricular septal defects. Additionally, there were 42 newborns with CHD who have no cardiac abnormality during the fetal period. It indicated that the screening of fetal echocardiography in CHD may cause missed diagnosis and overdiagnosis, which may lead to over induction. In our country, most pregnant women and families lack of the knowledge of CHD, reacting strongly to CHD in pregnancy, and eventually chose to give up due to severe psychological burden. Actually, several induction cases including congenital tricuspid regurgitation, small ventricular septal defects and left superior caval vein, maybe self-heal or effectively cured by surgery in later stage, and do not affect quality of life. For these

pregnant with fetal CHD, the ethics committee should strengthen management and strictly control the blind choice of induction.

We observed that pregnant women who have given birth to a child before have effect on the occurrence of CHD have less risk of having CHD in their offspring in comparison to the pregnant women who has never had a child before. (RR: 0.890; 95% confidence interval, CI, 0.813–0.975). We suspected that pregnant women who have given birth to a child before have more experience to take care of themselves in terms of diet, health and pre-pregnant check during pregnancy. Those pregnant women or their relatives had history of congenital heart disease increase odds ratio of having CHD in their offspring (RR, 2.480; 95% CI, 1.362–3.967), which is similar to the study done by Yokouchi-Konishi T, et al.²⁴ Some studies showed no association between maternal education level with CHD.²⁵ However, others have found that the occurrence of CHD was inversely associated with the mother's education level, and that there was a dose–response relationship between them.²⁶ In our study, as compared with maternal educational level group less than high school degree, in maternal educational level group high school or college degree, odds of having CHDs is 1.342 (RR, 1.390; 95% CI, 1.129–1.701). In China today, adolescents are becoming much more sexually liberated.²⁷ Premarital sex and unplanned pregnancies among teenagers are increasing, especially in the group of high school degree or college degree, thereby indirectly raising the occurrence of CHD. These findings also highlight the need to improve the healthcare and sex educational opportunities for teenagers, particularly for those with high school or college education. We found that those pregnant women who live in countryside induce odds ratio of having CHD in their offspring (RR, 0.821; 95% CI, 0.730–0.920). The main reason may be the complex industrial/urban scenario emission such as SO₂.²⁸ If pregnant women are influenced by environmental factors during this period (early trimester of pregnancy), the fetus easily suffers from CHD. In this study, we conduct a prospective cohort study of pregnant women and find that the odds of having CHD to be 1.214 (RR, 1.215; 95% CI, 1.080–1.359) with a history of illness in 1st trimester, which is similar to the study done by Liang Q, et al.²⁹ Poisson regression analysis indicated that twin and multi-fetal infants are more likely to suffer from CHD than singleton infants (RR: 1.631, 95% CI: 1.276–2.036). The study can examine the risk of CHD in twins compared with singletons. This is consistent with the study done by Best, K. and J. Rankin.³⁰ Our study found that the relative ratio of having CHD to be 1.780 (95% CI, 1.300–2.345) with birth defect in the firstborn child. The results indicate that the increased risk of CHD not only associate with the history of having a CHD sibling, but also with the history of having a birth defect sibling. Possible explanations for increased CHD risk in siblings of children with birth defect include shared genes, shared environmental factors, or a combination.³¹

Due to the registration process of the total pregnant women in Qingdao, we need multi-center cooperation to complete information collection throughout their pregnancy. There are more than 60 prenatal ultrasound institutions and many ultrasound physicians in the city. Owing to the widely different levels of experience of examiners, there is a large discrepancy in study results of second trimester ultrasound screening for fetal malformations, which is a result of varying levels of obstetric scanning expertise prevalent at the reporting center.

Conclusions

In conclusion, CHD among fetuses and infants are serious health problem in Qingdao, China, and the incidence of CHD was similar to existing research in Qingdao. Compared with neonate, the incidence of CHD is higher in fetal. Multi-fetal infants, greater than high school degree, illness in 1st trimester, family history of CHD and having a baby with birth defect before were correlated with an increased risk of CHD. Moreover, the risk factors were identified in our study, and our findings may have great implications of public health policy for CHD intervention in China.

List Of Abbreviations

CHD

congenital heart disease, QMCBDCP = Qingdao Municipal Center for Birth Defect Control and Prevention, QWCH = Qingdao Women and Children's Hospital, MRA = magnetic resonance angiography, SD = standard deviation, IQR = interquartile range, BMI = Body Mass Index, CI = confidence interval, RR = Relative ratio, NSFC = The National Natural Science Foundation of China

Declarations

Ethics: This study was approved by the Ethics Commission of Qingdao Women and Children's Hospital (QFFLL-KY-2020-11) and written informed consent was obtained from involved patients prior to enrollment.

Consent for publication: All authors provided critical feedback and approved the publication.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Conflict of Interest: none declared.

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Author Contributions: Q-SX, WN and G-JL designed the study and conceptualised the paper. XJ, WN, G-JL, G-LW, QW, JZ, NJ, WJC, QL and LG collected the epidemiological and clinical data. XJ summarised the data and conducted statistical analysis. XJ, WN and G-JL wrote the initial draft of the manuscript. All authors provided critical feedback and approved the final version. The corresponding author has full access to all data in this study and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Table 1 Risk factors of congenital heart defects on univariate analysis

Risk factors	CHD	No CHD	P value
Twinning	1031	62559	<0.001
Yes	37	1136	
Maternal age (years)			0.186
< 35	869	50782	
≥35	199	12913	
Maternal body mass index (BMI)			<0.001
<18.5	105	5164	
18.5-25	668	36534	
>25	179	11424	
Living location			<0.001
City	775	39499	
Countryside	199	15125	
Assisted reproduction	949	53878	0.005
Yes	24	765	
Maternal educational level			<0.001
< High school	150	11807	
High school degree or college degree	748	39857	
> College degree	76	2967	
Eating habits			0.595
Not partial	823	46586	
Eating less meat	124	6316	
Eating less vegetable	26	1721	
Paternal age (years)			0.762
≤30	463	25712	
>30	510	28884	
Number of previous pregnancies			0.007

0	341	17159	
1	349	19757	
>1	283	17730	
Fertility history			<0.001
0	513	25508	
≥1	460	29138	
History of having a child with birth defect	950	54065	<0.001
Yes	23	581	
History of illness in 1st trimester	795	46981	<0.001
Yes	179	7665	
Family history of birth defect	960	54262	0.007
Yes	14	384	
Family history of CHD	967	54554	<0.001
Yes	7	92	
History of folic acid intake			0.009
Don't eating folic acid	49	3374	
Eating folic acid 3 months before or 3 months after pregnancy	639	37044	
Eating folic acid 3 months before and 3 months after Pregnancy	286	14228	
History of husband smoking before			0.015
0	635	33466	
<10	167	10507	
10-19	114	6945	
≥20	58	3728	

Table 2 Prevalence of congenital heart disease in fetus and newborns by major ICD-11 categories according to fetal echocardiography and pregnancy outcomes in Qingdao prospective study

Congenital heart disease	ICD-11 code	Fetus n (%)	Termination n (%)	Newborns n (%)
Transposition of the great arteries	LA85.1	4 (0.39%)	4 (3.51%)	0 (0.00%)
Double outlet right ventricle	LA85.2	3 (0.29%)	2 (1.75%)	1 (0.21%)
Common arterial trunk	LA85.4	1 (0.10%)	1 (0.88%)	1 (0.21%)
Left superior caval vein	LA86.0	14 (1.36%)	1 (0.88%)	8 (1.71%)
Partial anomalous pulmonary venous connection	LA86.21	0 (0.00%)	0 (0.00%)	1 (0.21%)
Other specified anomalous pulmonary venous connection	LA86.2Y	37 (3.61%)	2 (1.75%)	21 (4.49%)
Congenital tricuspid regurgitation	LA87.00	302 (29.43%)	4 (3.51%)	88 (18.80%)
Ebstein's anomaly	LA87.0Y	1 (0.10%)	1 (0.88%)	0 (0.00%)
Congenital mitral regurgitation	LA87.10	7 (0.68%)	0 (0.00%)	3 (0.64%)
Atrioventricular septal defect	LA87.20	9 (0.88%)	6 (5.26%)	1 (0.21%)
Tetralogy of Fallot	LA88.2	29 (2.83%)	19 (16.67%)	4 (0.85%)
Ventricular septal defect	LA88.4	274 (26.71%)	12 (10.53%)	161 (34.40%)
Hypoplastic right heart syndrome	LA88.Y	3 (0.29%)	2 (1.75%)	0 (0.00%)
Hypoplastic left heart syndrome	LA89.3	4 (0.39%)	4 (3.51%)	0 (0.00%)
Functionally univentricular heart, unspecified	LA89.Z	6 (0.58%)	6 (5.26%)	0 (0.00%)
Congenital pulmonary valvar stenosis	LA8A.00	23 (2.24%)	3 (2.63%)	9 (1.92%)
Congenital pulmonary regurgitation	LA8A.01	53 (5.17%)	0 (0.00%)	22 (4.70%)
The dysplastic pulmonary valve	LA8A.0Y	2 (0.19%)	1 (0.88%)	1 (0.21%)
Congenital pulmonary atresia	LA8A.1	1 (0.10%)	0 (0.00%)	1 (0.21%)
Congenital aortic regurgitation	LA8A.21	2 (0.19%)	0 (0.00%)	1 (0.21%)
Bicuspid aortic valve	LA8A.22	1 (0.10%)	0 (0.00%)	1 (0.21%)
Coarctation of aorta	LA8B.21	17 (1.66%)	1 (0.88%)	17 (3.63%)
Interrupted aortic arch	LA8B.22	2 (0.19%)	1 (0.88%)	0 (0.00%)

Vascular ring	LA8B.2Y	77 (7.50%)	6 (5.26%)	54 (11.54%)
Congenital anomaly of great arteries including arterial duct, unspecified	LA8B.Z	9 (0.88%)	0 (0.00%)	9 (1.92%)
Congenital coronary arterial fistula	LA8C.2	3 (0.29%)	0 (0.00%)	2 (0.43%)
Divided left atrium	LA8G.0	1 (0.10%)	0 (0.00%)	0 (0.00%)
Restricted oval	LA8E.Y	12 (1.17%)	0 (0.00%)	0 (0.00%)
Multiple structural developmental anomaly of heart or great vessels	LA8Y	84(8.19%)	28 (24.56%)	62 (13.25%)
Structural developmental anomaly of heart or great vessels, unspecified	LA8Z	45 (4.39%)	10 (8.77%)	0 (0.00%)
Total	LA80- LA8Z	1026 (100%)	114 (100%)	468 (100%)

Figures

Figure 1

Subjects in this report and the distribution of CHD according to prenatal echocardiography in the second trimester and pregnancy outcomes

Figure 2

The incidence and distribution of CHD in fetal and neonatal

Figure 3

Risk factors of CHD on multivariate analysis conducted by Poisson regression model

Figure 4

Risk factors of congenital heart defects on Logistic regression analysis