A multicenter case-control study on non-genetic risk factors in infants with congenital heart disease

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Research article

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Abstract

Background: The incidence of congenital heart disease (CHD) is growing at a rapid speed worldwide, which due to changes of both environmental and lifestyle exposures. This study aimed to explore how the non-genetic risk factors of maternal and perinatal conditions influenced onset of CHD in infants.

Methods: Infants with congenital heart disease diagnosed by echocardiography from May 2012 to December 2013 were recruited as positive cases, while healthy individuals without congenital heart disease recruited at the same period were regarded as controls. The general situation of parents and the exposure to environmental factors during perinatal period in the case group and the control group were investigated by questionnaires.

Results: A total of 424 questionnaires of infants with congenital heart disease and 362 healthy controls were finally collected. We analyzed the risk factors during perinatal period of their mothers showed that their mothers took drugs in early pregnancy (odds ratio [OR]=4.41, 95 % confidence interval [CI]:2.41-6.73), viral infection (OR = 2.97, 95% CI: 1.62-5.73), house decoration (OR = 1.82, 95% CI: 1.43-3.75), hair dyeing and scalding (OR = 2.24, 95% CI:1.46-4.05), parents' exposures to work environment pollution (OR = 2.77, 95% CI: 2.03-5.38) were independent risk factors for cardiovascular malformations. With the increase of exposure factors, the risk of congenital heart disease increased significantly. When pregnant women were exposed to three or more risk factors at the same time, the risk of infants with congenital heart disease in was 17.24 times higher than that of single-factor exposure.

Conclusions: Together, the incidence of CHD in infants is correlated with the exposure to perinatal risk factors.

Background

Congenital heart defects (CHD) are one of the most common congenital malformation and fatal birth defects in newborns, with over a quarter will develop seriously to a term called critical congenital heart defect.^{1,2} According to the latest report of birth defects prevention and treatment in China, CHD has become the leading causes of the incidence of perinatal mortality since 2005.³ The long-term survival rates of CHD have increased greatly ascribed to recent progresses made in interventional therapies, surgical procedure and clinical diagnosis.^{1,4} The occurrence of congenital heart disease is a complex process, which involving the interaction among multiple factors, including genetic factors, polygenic inheritance and environmental factors.^{5,6} It confirmed that polygenic inheritance, i.e. the interaction between genetic factors and environmental factors, is the main responsible factor for congenital heart disease.⁷ Previous studies have shown that maternal exposure to viral infection during pregnancy, especially in the early period of pregnancy, radiation and the drug usage would heighten the risk of congenital heart disease.^{8,9} However, due to the differences in housing environment and lifestyle between various regions and populations, there are still some problems such as regional limitations and insufficient sample size in exploring the causes of CHD in China by non-genetic factors. This study

explored the relationship between non-genetic exposures during perinatal period and the incidence of CHD, in order to improve the understanding of environmental risk factors of perinatal couples and provide scientific basis for intervention measures to reduce the incidence of CHD.

Methods

Research cohorts

In this research, a multi-center clinical case-control investigation was conducted to collect infants with CHD diagnosed by echocardiography from May 2012 to December 2013. This study was with informed consent of their families. The case group included infants and young children with CHD (with phenotype of abnormal regional anatomy due to the formation of heart and large vessels, or failure to close the channels that should be automatically closed after birth). Exclusion criteria for cases were as follows: 1) Pregnant women's gestational weeks were less than 14 weeks; 2) Pregnant women had mental disorders or noncompliance; 3) Fetus were complicated with extracardiac malformations; 4) Fetal was complicated with chromosomal abnormalities, genetic syndrome, indefinite diagnosis or polyembryony; 5) Patent foramen ovale as well as patent ductus arteriosus were identified within 1 year of age. Infants with the same age and of the same period without congenital heart disease by ultrasonography and clinical diagnosis were enrolled as the control group. All the enrolled infants in the study group were all diagnosed again by the ultrasound department, pediatrics, gynecology and obstetrics department and pathologists in their hospital within 3 months after birth.

Research method

For parents of infants in both case group and control group, a questionnaire on risk factors of congenital heart disease in infants was filled out under the guidance of investigators. The main contents of the survey included: basic demographic characteristics of pregnant women and their husbands (nationality, height, weight, age, place of residence, educational level, occupation, etc.), general situation of infants and young children, history of drug exposure during pregnancy, history of viral infection during pregnancy, history of house decoration during pregnancy, history of hair dying and perm of pregnant mothers, working environment during pregnancy, life events, disease history and current medication profile, history, diet and nutrition, results of clinical examination and basic information of newborns. This study stipulated that fathers and mothers are engaged in chemical industry, wood processing, textile and house decoration for a long time (at least one year before pregnancy). Working in this environment for an average of more than 8 hours a day was regarded as work environmental pollution.

Statistical analysis

SPSS 20.0 was used for statistical analysis. The possible research variables related to CHD were determined. The t-test was used to compare the measurement data between groups, the 2-tail t test was used to compare the counting data between groups, and the multivariate logistic regression analysis was used to analyze the risk factors. P value < 0.05 was considered as significant difference.

Results

General Analysis

A total of 786 valid questionnaires were collected, including 424 cases in the experimental(case) group and 362 cases in the control group. The age range of pregnant women in case group was 17–42 years old, with an average of 27.51 years, while correspondent age in control group was 18–43 years old, with an average of 27.6 years. However, no statistically significant differences in age, nationality, gestational age, pregnancy history and education level were detected between the case group and the control group ($P > 0.05$). Notably, significant differences in the residence of parents and adverse pregnancy history of pregnant women were found ($P < 0.05$) between two groups. Among 424 CHD cases, 181 cases (42.69%) had conus arteriosus defect, 110 cases (25.94%) had septal defect, 10 cases (2.36%) had anomalous pulmonary venous drainage, 97 cases (22.88%) had right ventricular outflow tract obstruction or left ventricular outflow tract obstruction.

Association between Parental Risk Factor Exposure and Congenital Heart Disease in Infants

As shown in Table 2, Drug taken by mothers in early pregnancy, viral infection, house decoration, hair dyeing and perm during pregnancy or half a year before pregnancy, and environmental pollution of parents' work places are all independent risk factors for cardiovascular malformations.

Multivariate Logistic Regression Analysis regarding Risk Factors of CHD Infants

Among the subjects included in the study, women taking drugs in early perinatal period (OR = 4.41, 95% CI: 2.41–6.73), house decoration (OR = 1.82, 95% CI: 1.43–3.75), viral infection (OR = 2.97, 95% CI: 1.62–5.73), environmental pollution exposure of parents' work places (OR = 2.77, 95% CI: 2.03–5.38), hair dyeing and scalding (OR = 2.24, 95% CI: 1.46–4.05) and their associations with congenital heart disease were all shown in table 3.

Correlation between multiple factors and CHD

With the increase of exposure factors, the risk of congenital heart disease increased as well. When parents were exposed to three or more risk factors during pregnancy, the risk of CHD in infants was 18.03 times higher than that of single-factor exposure, as shown in Table 4.

Discussion

CHD is a polygenic hereditary disease, and it is mainly caused by both influences of embryonic heredity and environmental factors. ^{10,11} After fertilization, the 8 weeks period is an important stage for embryonic development, cell proliferation and differentiation processes are vulnerable to external factors. ¹² An abundant number of data showed that maternal exposure to viral infection, radiation and medication during pregnancy, especially early pregnancy, increased the risk of congenital heart disease. ^{13,14}

This study retrospectively analyzed the exposure of common risk factors in mothers' living and working environment one year before and after pregnancy, and assessed the risk of developing fetal congenital heart disease.¹⁵ The results indicated that maternal medication in early pregnancy, viral infection, hair dyeing and perm during pregnancy or half a year before pregnancy, house decoration, parents' exposure to environmental pollution are independent risk factors for congenital heart disease in infants and young children.^{16–18} Multivariate logistic regression analysis showed that the incidence of CHD was associated with hair perm and dyeing, medication taken by mothers in early pregnancy, house decoration, virus infection, and exposure to pollution of working environment.¹⁹ Viral infections and medicines used in early pregnancy have been considered as a vital factor of developing congenital cardiovascular disease.²⁰ Many studies have shown that the usage of drugs has certain impact on congenital heart disease, such as anti-infective drugs, sulfonamides have significant impact on the normal development of cardiovascular system, but the relationship between penicillin and congenital heart disease is not certain.^{21,22} Antiasthma, antidepressant, antifungal drugs and drugs for treating hypertension and hypothyroidism all increased the incidence of congenital heart disease.²³ Several large-scale studies have shown that pregnant women who took progesterone, amphetamine, anticancer drugs and methionine in the early pregnancy significantly increased the risk of developing CHD in their offspring.²⁴ The intake of hormones during pregnancy increased the risk of CHD in the fetus, such as intake of progesterone in the early pregnancy and ventricular septal defect in the offspring had over 5 times higher risk of developing CHD than those in the control group.²⁵ Early use of erythromycins, non-steroidal anti-inflammatory drugs and drugs for thyroid diseases in pregnant women would lead to CHD in their offspring.²⁶ This study showed that drug use in early pregnancy is a more sensitive teratogenic factor than other factors among various analysis factors.

It has been reported that formaldehyde and other harmful substances emitted from decoration materials can still be detected within 2 years. These substances would seriously pollute the indoor air and affect the growth and development of the fetus through the placental barrier, thus causing developmental malformation.²⁷ The results of this study showed that living in a house renovated for one year during pregnancy increased the risk of congenital heart disease, which is consistent with domestic and foreign research reports. The results of this study explored the relationship between decoration pollution and congenital heart disease, suggesting that perinatal exposure to decoration pollution is a significant risk factor for CHD.

Exposure to chemical pollution is another risk factor that should not be ignored. Studies have shown that occupational chemical contamination may cause abnormal development of embryos after fertilization by deteriorating the quality of fathers' sperm and interfering with gene replication during sperm maturation.²⁸ With the development of society, especially in developing countries, chemical pollution is not limited to special occupational areas, but with the use of inferior raw materials in building decoration and processing industries, many pollutants are increasingly used in the daily work and living environment of people rapidly.²⁹ This study analyzed the relationship between cumulative exposure to risk factors and

the incidence of congenital heart disease. The results showed that with the increase of exposure factors, the incidence of CHD increased correspondently.

Conclusion

However, some limitations existed in this study due to experimental condition. Since that it was a retrospective investigation, the exclusion and diagnosis of cases and controls only depend on ultrasound diagnosis and clinical diagnosis, which may have a partial impact on the results. In addition, there is a memory bias in the survey of parents' risk factors exposure of infants and young children, and some of the respondents cannot accurately review the dosage of drugs taken at the time of pregnancy and the date of specific use. For the investigation on parents' exposure to risk factors, because the quantitative value of indoor pollution indicators in early pregnancy cannot be obtained, there is no further quantitative assay of the degree of pollution. Therefore, the analysis of the results may underestimate the impact of indoor pollution on the incidence of CHD.

Abbreviations

congenital heart disease (CHD); odds ratio (OR), confidence interval (CI).

Declarations

Ethics approval and consent to participate

All patients signed an informed-consent document for diagnosis and research on tissue specimens before being enrolled in the project. All subjects gave written informed consent in accordance with the Declaration of Helsinki principles. The protocol was approved by the Ethics Committee of the Renmin Hospital of Wuhan University.

Consent for publication

Informed consents were obtained from all individual participants included in the study.

Availability of data and material

The authors declared that the relative data supporting all the findings of this investigation are available within the article.

Competing interests

The author declared that they have no competing interest.

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Authors' contributions

Conceptualization: TQZ

Methodology & Investigation: YW, HS

Formal analysis: DXL, HS

Funding acquisition: TQZ

Project administration: TQZ

Supervision: TQZ

Validation: ZTQ

Writing - original draft: YW

Writing - review & editing: TQZ

All authors have read and approved the manuscript.

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Tables

Table 1 The basic age and education situation of parents

Variable	Case	Control	χ^2	P
Age of father (year)			4.74	0.023
≤35	345(81.4)	270(74.6)		
≥35	79(18.6)	92(25.4)		
Age of mother (year)			1.82	0.317
≤35	364(85.8)	316(87.3)		
≥35	60(14.2)	46(12.7)		
Education degree of father			51.64	0.001
<junior middle school	135(31.8)	67(18.6)		
senior high school/ polytechnic school	226(53.3)	164(45.3)		
>junior college	63(15.1)	131(36.2)		
Education degree of mother			47.58	0.001
<junior middle school	147(34.7)	60(16.6)		
senior high school/ polytechnic school	206(48.6)	169(46.7)		
>junior college	71(16.7)	133(36.7)		

Table 2 Association between risk factors exposure and congenital heart disease

Variable	Case	Control	χ^2	P	OR (95% CI)
Drug			46.37	0.001	
Y	71 (16.7)	19 (5.2)			1.00
N	353 (83.3)	343 (94.8)			4.41 (2.41-6.73)
Virus infection			12.69	0.001	
Y	36 (8.5)	12 (3.3)			1.00
N	388(91.5)	349 (96.4)			2.97 (1.62-5.73)
House decoration			11.04	0.001	
Y	69 (16.3)	31 (8.6)			1.00
N	355 (83.7)	331 (91.4)			1.82 (1.43- 3.75)
Hair dye			14.13	0.001	
Y	49 (11.6)	25 (6.9)			1.00
N	375 (88.4)	337 (93.1)			2.24(1.46-4.05)
Work environment pollution exposure			27.58	0.001	
Y	75(17.7)	25 (6.9)			1.00
N	349(82.3)	337 (93.1)			2.77 (2.03-5.38)

Table 3 Multivariate Logistic regression analysis

Variable	β	Sx	Wald	P	OR (95% CI)
Drug administration	1.37	0.24	30.13	<0.001	4.00 (2.51-6.73)
Virus infection	0.86	0.21	5.84	0.013	2.32 (1.16-5.21)
House decoration	0.58	0.33	5.73	0.019	1.67 (1.23-2.48)
Hair dye	0.57	0.26	5.64	0.017	1.79 (1.16-2.56)
Work environment pollution exposure	0.85	0.27	15.95	0.001	2.73 (1.72-3.70)

Table 4 Association between cumulative exposure factors of parents and congenital heart disease of infants

n	Case	Control	OR (95% CI)	P
0	226 (53.3)	281 (77.6)	1.00	<0.001
1	121 (28.5)	69 (19.1)	1.96 (1.38-3.52)	<0.001
2	41 (9.7)	9 (2.5)	6.05 (3.14-11.62)	<0.001
≥ 3	36 (8.3)	3 (0.8)	17.35 (5.13-57.86)	<0.001

Supplementary Files

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