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Clinical screening method and risk factors' analysis of congenital cardiovascular defects: a case control study from a Chinese local region

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Summary

Aim: To explore the effective clinical screening method and risk factors of congenital heart disease (CHD) in neonates. *Materials and Methods:* The authors screened neonatal congenital heart diseases using eight clinical screening indexes and analyzed to acquire the simplest and most effective screening method. They also conducted a hospital-based 1:1 matched case (total 64 cases) – control study to analyze a series of underlying risk factors. *Result:* The eight clinical indexes are reliable screening means. The main risk factors influencing the incidence of CHD in the present samples were abnormal reproductive history ($p = 0.008$), negative stimulus ($p = 0.075$), upper respiratory infection ($p = 0.06$), diabetes mellitus ($p = 0.058$), high blood pressure ($p = 0.041$), husband's cigarette smoking ($p = 0.001$), and gravidity ($p = 0.000$). *Conclusion:* The eight clinical indexes were reliable means to screen CHD in neonates. Eliminating abortion or other abnormal reproduction, augmenting maternal mental healthcare, preventing upper respiratory tract infections, limiting medication during early pregnancy including antihypertensive agent, controlling blood glucose levels, and abstaining from cigarette may lower the occurrence of CHD.

Key words: Congenital heart disease; Risk factors; Case control study.

Introduction

Congenital heart disease (CHD) is a serious threat to public health [1] and remains a leading cause of childhood morbidity and mortality. Unfortunately, CHD is common worldwide, with an incidence of approximately 1% and consequently is a major health concern [2]. Screen, follow-up, assessment, and intervention system of newborn CHD disease has not been established. Appropriate preoperative diagnosis and optimized perioperative treatment scheme can improve survival rate and life quality. About 80% of CHD is multifactorial and arises through various combinations of genetic and environmental contributors [3]. The definite mechanism is not yet clear and the primary prevention system has not be established.There are some reports illuminating various risk factors, such as maternal age drug application [4], and molecular pathways, but there is no consolidated answer. On the other hand, affected neonates of ethnic Han in China account for a high proportion for total patients in the world. The prevalence is seven to eight per 1,000 live births in China, which represents approximately 100,000 to 150,000 new cases of CHD per year [5]. However researches aiming at Chinese CHD morbidity are relatively less. The present study analyzed the correlation between many potential risk factors and the occurrence of the CHD. The authors hope this study can provide some evidence for the prevention of CHD.

Materials and Methods

Selection of participants

The authors screened neonatal CHDs using eight clinical screening indexes (including family history of CHD, abnormal fetal heart Doppler ultrasound, dyspnea, cyanosis, special faces, cardiac auscultation, neonatal congenital malformations, and blood oxygen saturation) in 5,965 newborns and found 75 positive indexes cases (1.26%). Then 43 cases were diagnosed by echocardiography and 0.32 (5.36%) were diagnosed as CHD. The screened 43 cases were confirmed as CHD at the end of 12-month follow-up (Figure 1, Table1).

The authors chose 32 healthy cases as the control group and performed a retrospective cohort study involving the collection of data from a maternal and child health hospital in Taian. CHD diagnosis standard used Doppler ultrasound results as a diagnosis standard, arterial duct unclosed in three months or more, and oval foramen patency in one year or more.

The following exclusion criteria [6] were used (group1): 1) diagnosed as syndromic CHD caused by gene mutation or chromosomal aberration; 2) patient's natural parents dead or natural mother dead; 3) patient's natural parents divorced; 4) patient's natural parents or mother not present; 5) unwillingness to accept investigation; 6) presence of abnormalities in other organs

The control group (group 2) was matched to the study group by the following criteria:1) the same sex; 2) age (± one year); 3) without CHD or any other birth defects by unified diagnosis

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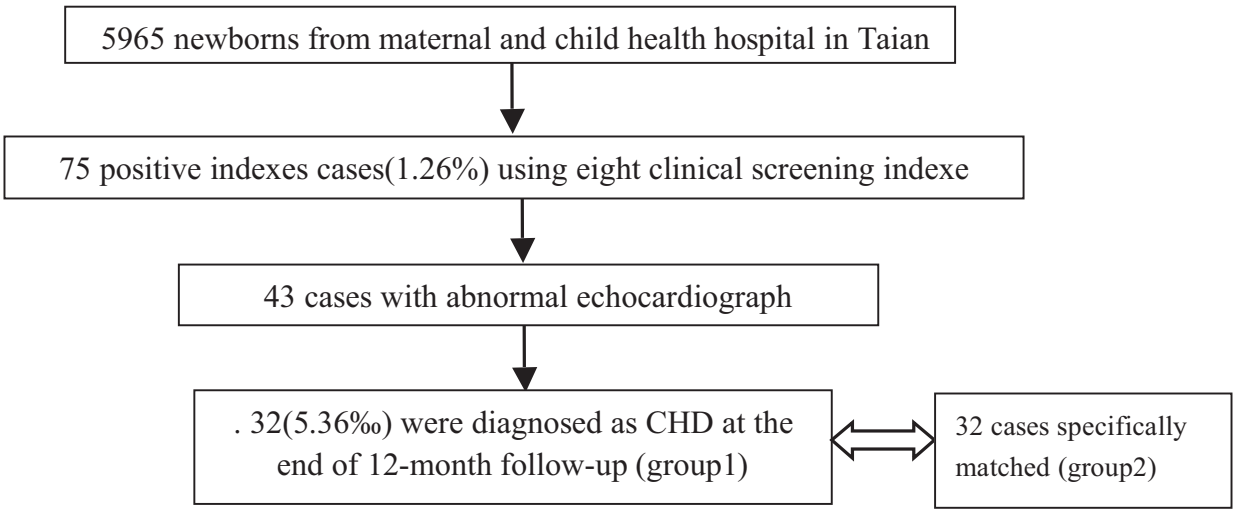

Figure 1. — Database search pathway and group division. Neonatal CHDs were screened using eight clinical screening indexes (including family history of congenital heart disease, abnormal fetal heart Doppler ultrasound, dyspnea, cyanosis, special faces, cardiac auscultation, neonatal congenital malformations, and blood oxygen saturation) in 5,965 newborns and found 75 positive indexes cases (1.26%). Then 43 cases were diagnosed by echocardiography and 0.32 (5.36%) were diagnosed as CHD. The screened 43 cases were confirmed as CHD at the end of 12-month follow-up.

Table 1. — *Risk factors correlation analysis.*

Risk factors		Study group {n. (%)}	Control group {n. (%)}	*p*
Maternal illnesses and conditions	Diabetes mellitus	14/32 (43.75%)	6/32 (18.75%)	0.058
	Upper respiratory infection	12/32 (37.50%)	3/32 (9.38%)	0.060
	High blood pressure	12/32 (37.50%)	4/32 (12.50%)	0.041
	Diarrhea	6/32 (18.75%)	4/32 (12.50%)	0.474
	Hepatitis B	2/32 (6.25%)	4/32 (12.50%)	0.672
	Skin rash	5/32 (15.63%)	3/32 (9.38%)	0.708
	Psychiatric history	6/32 (18.75%)	1/32 (3.13%)	0.104
Female hormones	Oral contraceptive	5/32 (15.63%)	3/32 (9.38%)	0.708
	Ovulation stimulating drug	4/32 (12.50%)	1/32 (3.13%)	0.196
	Progesterone	6/32 (18.75%)	2/32 (6.25%)	0.257
Maternal drinking and smoking	Alcohol	2/32 (6.25%)	3/32 (9.38%)	1.000
	Cigarette Smoking	1/32 (3.13%)	0/32 (0.00%)	1.000
Maternal environmental exposures	Environment pollution	5/32 (15.63%)	1/32 (3.13%)	0.196
	Pesticide contact history	2/32 (6.25%)	0/32 (0.00%)	0.492
Maternal socio-demographic characteristics	Age (years)	25.30 ± 3.46	25.83 ± 5.18	0.333
	Negative stimulus	11/32 (34.38%)	4/32 (12.50%)	0.075
	Abnormal reproductive history	17/32 (53.13%)	6/32 (18.75%)	0.008
	Gravidity (n.)	1.91 ± 0.79	1.53 ± 0.89	0.000
Nutrition	Folic acid	20/32 (62.50%)	24/32(75.00%)	0.419
Paternal exposures	Husband's cigarette smoking	27/32 (84.38%)	13/32 (40.63%)	0.001
	Husband's drinking	23/32 (71.88%)	17/32 (53.13%)	0.196

standard. Controls were also excluded for the aforementioned criteria { 2) - 6) }.

Data collection and management

One interviewer conducted face-to-face interviews of the participant's birth parents using a standardized questionnaire. The questionnaire included following content:

1) Demographic characteristics: child's name, sex, birth date, address, and nationality.
2) Maternal illnesses and conditions: diabetes mellitus, upper respiratory infection diarrhea, hepatitis B, skin rash, high blood pressure, and psychiatric history.
3) Female hormones contact history: oral contraceptive, ovulation stimulating drug, and progesterone.
4) Maternal non-therapeutic drug exposure: alcohol, and cigarette smoking.
5) Maternal environmental exposures: environment pollution and pesticide contact history.
6) Maternal socio-demographic characteristics: age, negative stimulus, abnormal reproductive history, and gravidity

Table 2. — *Ratio of different indexes and combination in CHD*

Method	75 positive indexes cases n. (%)	43 abnormal echocardiography n. %	32 diagnosed CHD n. %	4 complex CHD n. %
Family history of CHD	1 (1.33)	1 (2.32)	1 (3.33)	0 (0.00)
Abnormal fetal heart Doppler ultrasound	10 (13.33)	10 (23.26)	10 (33.33)	1 (25.00)
Dyspnea	16 (21.33)	10 (23.26)	6 (20.00)	4 (100.00)
Cyanosis	20 (26.67)	12 (27.91)	4 (13.33)	3 (75.00$^{\Delta}$)
Special faces	6 (8.00)	4 (9.30)	4 (13.33)	1 (25.00)
Cardiac Auscultation	32 (42.67)	27 (62.79)	23 (76.67*)	4 (100.00)
Neonatal congenital malformations	9 (12.00)	6 (13.95)	4 (13.33)	2 (50.00)
Blood oxygen saturation	36 (48.00)	28 (65.12$^{\#}$)	22 (73.33$^{\#}$)	4 (100.00)
Abnormal fetal heart Doppler ultrasound + cardiac auscultation + blood oxygen saturation	53 (70.67$^{\#}$)	40 (93.02)	30 (100)	4 (100.00)
Cardiac auscultation + blood oxygen saturation	52 (69.33)	39 (90.68$^{\Delta}$)	3 0(100)	4 (100.00)

$^{\#}$ $p < 0.01$; * $p < 0.05$; $^{\Delta}$ $p > 0.05$.

7) Nutrition: folic acid.
8) Paternal exposures: husband's cigarette smoking and husband's drinking.

All data entry was completed independently by two external staff members and a database was established using Excel 2003.

Definitions

These included maternal illnesses and conditions of disease history in early pregnancy. Abnormal reproductive history included history of abortion, stillbirth, and fetal malformation. Negative stimulus included relatives' morbidity or death, dissociation, unemployment, and so on. Environmental factors included air and water pollution.

The present study included the following risk factors: abnormal reproductive history, negative stimulus, upper respiratory infection, husband's cigarette smoking and drinking history, diabetes mellitus, high blood pressure, gravidity, oral contraceptive, ovulation stimulating drug contact history, progesterone contact history, folic acid, smoking and drinking history, diarrhea, skin rash, hepatitis B, psychiatric history, environment pollution, pesticide contact history, and maternal age (Table 2).

Statistical analysis

Statistical analysis was performed using SPSS17.0, taking into consideration a match between each study case and control. For continuous variables (age and gravidity), the difference between the case and the mean of the control was computed and tested with a *t*-test for paired comparisons. For proportions, the Chi-square test or Fisher's exact test was applied to obtain group comparisons. Data are presented as mean ± SD (standard deviation). The two-tailed *p*-value < 0.1 was considered significant. Baseline characteristics that were found to differ between the groups ($p < 0.05$) were entered into two-category models to control for confounders.

Table 3. — *Sensitivity, specificity, and positive predictive and negative predictive values of different indexes combination application in neonatal CHD screening.*

Method	8 screening indexes %	3 screening indexes %	2 screening indexes %
Sensitivity	94.12$^{\Delta}$	94.12	91.42$^{\Delta}$
Specificity	99.28	99.28	99.28
Positive predictive value	42.67	42.67	42.67
Negative predictive value	99.97	99.97	99.97

Sensitivity comparison of 8 screening indexes and 2 screening indexes: $^{\Delta}$ $p > 0.05$.

This study was approved by the Institutional Review Board (IRB) of Taian Maternal and Child Health Hospital. Written informed consent was obtained from the participants at the time of presentation.

Results

The effective clinical screening method

The sensitivity, specificity, positive predictive, and negative predictive value of eight clinical indexes, respectively, were 94.12%, 99.28%, 42.67%, and 99.97% (Table 3). The combination of three indexes could have achieved the same sensitivity, specificity, positive predictive and negative predictive value. The composition of two indexes (cardiac auscultation + blood oxygen saturation) could have reached the approximate sensitivity (91.42%) and this screening method could also have achieved the same specificity, positive predictive, and negative predictive value compared to eight clinical indexes screening.

Characteristics of cases and controls

According to the present results, negative stimulus, abnormal reproductive history, upper respiratory infection, husband's cigarette smoking, diabetes mellitus, high blood pressure, and gravidity were significant harmful elements.

Maternal illnesses and conditions were connected with the CHD incidence rate, especially to exposure of those diseases: diabetes mellitus ($p = 0.058$), upper respiratory infection ($p = 0.060$), and high blood pressure ($p = 0.041$). The expectant mothers with diabetes mellitus accounted for a relatively large percentage (43.75%). Contact history to female hormones history had no significance relation to cardiovascular system defects. Alcohol or cigarette smoking was not relevant. The authors found no meaningful difference between two groups with regards to environment pollution and pesticide contact history, which is in contrast with some studies. Apparently, maternal socio-demographic characteristics played an important role in pathogenesis of CHD. It showed that negative stimulus, abnormal reproductive history, and higher number of pregnancies were absolute risk factors.

Discussion

The effect screening method

There is a large sample prospective study in China exploring simple screening method of CHD [7]. It reported that pulse oximetry plus clinical assessment is feasible and reliable in the detection of major CHD in newborn babies in China. The eight clinical indexes were reliable means to screen CHD in neonates. Combination of neonatal cardiac auscultation, abnormal fetal heart Doppler ultrasound, transcutaneous oxygen saturation, and combination of cardiac auscultation and transcutaneous oxygen saturation had the same sensitivity as the eight indexes and should be extended.

Upper respiratory infection, especially febrile illnesses such as flu-associated fever was closely related to CHD. One possibility mechanism is altered apoptosis. Apoptosis is known to be involved in cardiac morphogenesis, for example, in the development of the cardiac outflow tract [8], and can be altered by both fever and infection [9]. Another possibility is a direct effect of the underlying virus infection. The evaluation of the safety of non-steroidal antiinflammatory drugs requires more efforts.

With regards to diabetes mellitus, it is reported that offspring of women with pregestational diabetes mellitus are at increased risk for congenital malformations, largely attributable to poor periconceptional glycaemic control [10]. Therefore the present authors recommended that the patients plan pregnancy with lowerer blood glucose levels.

The association of cardiac defects with the use of antihypertensive medication, observed in the present study, was described as uncertain in the literature [11]. Antihypertensive agent plays an important part. Angiotensin enzyme converting inhibitors was recently identified as potentially teratogenic [12]. Other drugs such as diuretics and calcium channel blockers also had toxic and side effects. Gestational hypertension is a common complication. Appropriate physical exercise and healthy lifestyle may be a suggestion.

Pregnant women who also have a psychiatric history are confronted with a high risk of CHD.

Hepatitis B, diarrhea, and skin rash are not dangerous factors and there are few studies focusing on these factors. For some drugs and medicine exposure, the data in the present study is insufficient to be considered as a risk.

The effect of oral contraceptive has not yet been defined. Some studies showed that exposure to these drugs during the early period of pregnancy would lead to CHD [13]. However some reports obtained the opposite result [14]. It seems that ovulation stimulating drug and progesterone had no significant influence on the abnormality in the present statistical result. The present authors believe that female hormone contact or therapy history is a relatively safe factor.

One study conducted in southern California reported possible increased risks of aortic artery and valve anomalies with increased levels of ambient air levels of ozone during the second month of pregnancy [15]. Ground water contamination and water chlorination byproducts are risk factors [16].

Another study suggested that there is an association of maternal employment in the agricultural industry with an increased risk of conotruncal defects which implied that chemicals used in agriculture were teratogenetic [17]. Organic solvents and other pesticides can directly block replication of DNA and chromosome and the fetal toxicity is obvious and several case control studies also certify this [18].

Maternal socio-demographic characteristics

The results in this study are not consistent with the previous researches. In reality, CHD occurrence rate augment with an increase in age [19]. Moreover, the study of exact molecular mechanism is being carrying out. Transcription factor NKX2-5 is associated with malformation [20].

Maternal periconceptional stressful life events are associated with risks of the studied birth defects [21]. Exposure to negative stimulus may prompt pregnant women to produce more glucocorticoid which is associated with fetal malformation [22]. Other abnormal endocrine could lead to deformity [23].

Abnormal reproductive history is another important risk factor as reported in the current study [24]. There are some reasons responsible for it. Spontaneous abortion or stillbirth are the result of natural selection due to chromosomal defect; the expectant mother who experienced abortion would become more stressed. Surgical or medical abortion can both destroy muscular layer of endometrium which increases abortion probability. Negative previous history could also affect the uterus microenvironment and easily induce endometritis.

The number of previous pregnancies is an absolute factor associated with number of spontaneous abortions [25]. Multiparity has been limited in China since the family planning policy was implemented. We should exclude the miscarriage history and analyze the relation of gravidity and teratogenicity.

It has been confirmed that use of multivitamins containing folic acid was associated with a reduction in risk for congenital heart defects [25]. Folic acid supplement is of benefit to fetal development and it is a protective factor for CHD. The intake of folic acid lacks was indifferent in the present study. The authors speculate it is caused by small sample size and to an improved nutrition consciousness.

In the present study, husbands' smoking was a risk factor compared to maternal smoking due to the fact that there are a few Chinese women that smoke. In fact, husband' smoking or maternal smoking history does lead to high CHD incidence rate. Maternal smoking increased the risk for a number of congenital malformations and not only CHD [26]. Future smoking cessation programs should focus on

Table 4. — *Types of CHDs.*

Type of CHS	Numbers	Percentage (%)
Pure patent ductus arteriosus	6	27.27
Ventricular septal defect + patent oval foramen	16	50.00
Patent oval foramen + patent ductus arteriosus	4	12.50
Pure interatrial septal defect	1	3.13
Ventricular septal defect + interatrial septal defect	19	59.36
Interatrial septal defect + patent ductus arteriosus	20	62.50
Interatrial septal defect + patent oval foramen	22	68.75
Others	4	12.50

this adverse health aspect in order to encourage more women to quit smoking before or during early pregnancy.

Alcohol intake in the first trimester of pregnancy, as found in the present study, has been associated with the risk for heart defects [27]. As for the fathers, alcohol can reduce sperm quality. It is commonly known that men should cut out smoking and drinking three months prior to fertility. Alcohol intake increases oxidative stress and interferes with the normal process of programmed cell death [28].

Strengths and weakness of the present study

The present study screened a large number of patients and made a comprehensive analysis of potential risk factor. They conducted scientific statistical methods and obtained a credible conclusion. The present results are meaningful to clinicians and pregnant women which can assist them to prevent CHD. The strict matching procedures are one of the most important strengths of this study. Control groups were specifically chosen so that confounding variables were eliminated. As many other studies are uncontrolled (or historically controlled) and have small sample sizes. In the condition that national data collection is impossible, the present study nonetheless provides a reference for clinicians. There were some limitations to this study: sample content was relatively small so that some risk factors could not be defined. The data cannot represent the total distribution of CHD occurring in the local population. Secondly, the authors collected information by means of self-reporting, which was easier to implement results in recall bias. The respondents may also have not have provided exact information.

Implications for further research

The causes of CHD are multifactorial and the types of CHD are varied and complex (Table 4). Different risk exposure may be associated with different types of CHD. As for the certain risk factor, the molecular or genetic mechanism is in the agenda of future study and extensive epidemiological research and data collection are the eternal pursuit of the goal.

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