CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Preliminary analysis of risk factors for congenital heart disease: a retrospective review of 145 cases in a single institution

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Summary

Background: Congenital anomaly is one of the most common cause of infant mortality and in China the incidence is quite high compared to other countries. It is therefore important to identify the potential risk factors of congenital problem such as congenital heart diseases. *Materials and Methods:* A retrospective study of 5,636 newborn cases from 2012 to 2014 in Panyu Maternal and Child Care Service Centre of Guangzhou was carried out, and among which 145 cases were confirmed for congenital heart defects. Review and analysis of maternal and paternal factors was performed using univariate and multivariate logistic regression analyses. *Results:* Several maternal factors were significantly associated with the occurrence of the congenital anomaly. However, after combining both maternal and paternal factors, only higher maternal age (OR = 1.076, 95% CI: 1.007-1.148, $p = 0.029$) and increased gravidity (OR = 1.153, 95% CI: 1.024-1.298, $p = 0.018$) were identified as risk factors whereas RBC count (OR = 0.374, 95% CI: 0.187-0.745, $p = 0.005$) was identified as a protective factor of the abnormal outcome using multivariate regression analysis. *Conclusion:* Further investigation on how the level of RBC in mother may contribute to the prevention of congenital heart disease is warranted.

Key words: Congenital heart disease; Regression analysis; Maternal factor; Paternal factor; Retrospective analysis; Red blood cell count.

Introduction

Congenital anomaly requiring medical care constitutes approximate three percent of newborns and congenital cardiovascular defect is the leading cause of death [1-3]. In many countries including China, the contribution of birth defects to infant mortality has been increasing [4, 5]. Congenital heart disease is one of the most common birth defects with an incidence of 4 to 8 per 1,000 live births [4, 6, 7] and in China, the prevalence of congenital heart disease is 7 to 8 per 1,000 live births [8]. However, with improvements in prenatal diagnostic techniques and awareness of the importance of periconceptional folic acid supplementation, the incidence of neural tube defects has decreased significantly [9].

Investigation of modifiable risk factors attributable to heart defects has long been the focus of epidemiological research [10-12] and approximate 30% of the potentially modifiable factors were deemed contributing to some type of defects [13]. Currently, there is data showing contributing factors for different types of heart disease varies and regional differences in environmental risk factors were observed [14-16]. However, population-based data on non-inherited risk factors is still lacking and there is no reliable information available for developing preventive strategies.

The purpose of this retrospective study was to explore the relationship between non-inherited risk factors and congenital heart diseases through reviewing the medical records and collecting relevant data between 2012 and 2014. The study mainly focused on investigating maternal and paternal risk factors, as well as other factors identified during pregnancy follow-up.

Materials and Methods

This is a retrospective study of all born newborn cases in Panyu Maternal and Child Care Service Centre of Guangzhou. All data were retrieved from the hospital maternal care database and no special exclusion criteria was included in this study. Each case was identified by the name, gender, date of birth and bodyweight of the newborn baby and the information obtained from pregnancy follow-up was identified by the mother's name and date of follow-up. After excluding all duplicate records, each newborn case was matched with the maternal and paternal information, as well as the relevant clinical information obtained during pregnancy follow-up. Any case with missing data was not included for statistical analyses.

Maternal baseline data collected included maternal age, Chinese ethnic group, census data, mother's height, pre-pregnancy weight, mother's education level, and family income. Maternal and delivery histories were also collected, which included gravidity, parity, and history of induced abortion, spontaneous abortion, threatened abortion, preterm birth, and still birth. Mother's work environment classified as high risk including the workplace with high temperature, loud noise, dusty environment, peculiar smell, and those with exposure to chemicals, heavy metal and ionizing radiation, as well as contact with organic solvents were compared;

Revised manuscript accepted for publication July 16, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 5, 2019
doi: 10.12891/ceog4711.2019

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Published: 10 October 2019

Table 1. — *Comparison of maternal baseline characteristics between normal and abnormal fetal groups.*

Characteristics	Normal fetal group (n=5236)	Abnormal fetal group (n=145)	Total (n=5381)	t/χ^2	*p*
Age in years, mean (SD)	27.0 (5.3)	28.4(5.3)	27.1(5.3)	-3.054	0.002
Ethnic group, *n* (%)					
Han	5064 (96.7)	142 (97.9)	5206 (96.7)	0.485	0.486
Others	117 (2.2)	2 (1.4)	119 (2.2)		
Unknown*	55 (1.1)	1 (0.7)	56 (1.0)		
Census, *n* (%)					
Permanent residents	3603 (68.8)	94 (64.8)	3697 (68.7)	1.014	0.314
Floating population	1603 (30.6)	50 (34.5)	1653 (30.7)		
Unknown*	30 (0.6)	1 (0.7)	31 (0.6)		
Height cm, mean (SD)	158.50 (5.05)	158.14 (4.60)	158.49 (5.04)	0.832	0.406
Pre-pregnancy weight in kg, mean (SD)	50.88 (8.29)	51.23 (8.12)	50.89 (8.29)	-0.500	0.617
Education level, *n*(%)					
Less than primary school	71 (1.4)	4 (2.8)	75 (1.4)	11.448	0.043
Junior high school	1419 (27.1)	52 (35.9)	1471 (27.3)		
Senior high school	1640 (31.3)	42 (29.0)	1682 (31.3)		
College	1281 (24.5)	33 (22.8)	1314 (24.4)		
Undergraduate	741 (14.2)	11 (7.6)	752 (14.0)		
Postgraduate or above	65 (1.2)	3 (2.1)	68 (1.3)		
Unknown*	19 (0.4)	0 (0.0)	19 (0.4)		
Family income in CNY, mean (SD)	4138.66 (4223.54)	3521.55 (2467.71)	4122.03 (4186.93)	2.896	0.004

**Missing data are not included in statistical comparison between groups.*

however details of the distribution were not displayed. Other maternal factors identified during pregnancy were also studied, which included exposure to drugs/substances (e.g. antibiotics, antipyretic analgesics, NSAID, tocolytic, anticancer drugs, vitamin A, birth control pills, etc.), supplementation (e.g. folic acid and multivitamins), and other environmental exposure (e.g. toxic or harmful substances, X-ray irradiation, B-mode USG examination, electromagnetic radiation, ionizing radiation and high-intensity noise). Other routine assessments of vital signs and laboratory tests during pregnancy were also included in this retrospective review. Paternal data were also collected, which included the followings: paternal age, history of congenital heart disease or others, father's education level and occupation, previous risk of work environment, smoking and drinking habit, history of drug abuse, and previous exposure to X-ray irradiation, electromagnetic radiation, ionizing radiation, high-intensity noise, heavy metals, organic solvents, and pesticides.

All numerical data were expressed as mean (standard deviation) and were compared between groups using *t*-test for independent samples. If normality was not met, the medians were described and compared using non-parametric test. Count data were compared using Pearson χ^2-test or Fisher's exact test. Non-parametric Mann-Whitney U test was used for data not normally distributed. Statistically significant individual factors identified from univariate logistic regression analysis were included in the subsequent multivariate conditional logistic stepwise regression analysis to confirm the independent risk or preventive factors for congenital abnormality. Statistical analyses were performed using SAS9.4. *P*-values of less than 0.05 were considered statistically significant in this study.

This study was approved by Medical Ethics Committee of China Panyu He Xian Memorial Hospital, No. Panhetong 201224. This study also obtained signed informed consent from all participants.

Results

A total of 5,636 newborn cases in Panyu Maternal and Child Care Service Centre of Guangzhou were retrospectively reviewed. Among which, 145 cases were diagnosed congenital cardiac diseases. The three major cardiac diseases consisted of patent ductus arteriosus (n=39), atrial septal defect (n=15), and perimembranous ventricular septal defect (n=13). Compared to the normal newborns (n=5482), the gestational age of abnormal newborns was significantly lower than that of normal newborns (35.01 ± 5.83 weeks *vs*. 38.60 ± 1.72 weeks, $p < 0.001$) and the average weight was also significantly lower (2525.47 ± 1050.56 g *vs.* 3152.08 ± 457.83 grams, $p < 0.001$).

According to univariate logistic regression analysis of 5,381 evaluable cases, the following maternal factors were statistically associated with the congenital abnormality: maternal age, education level, occupation, previous work at high-risk factories, passive smoking, alcohol drinking, gravidity, history of induced abortion, history of spontaneous abortion, history of threatened abortion, folic acid supplementation before or during pregnancy, exposure to toxic or harmful substances before or during pregnancy, previous use of birth control pills, tocolytic drugs, vitamin A and other drugs (including traditional Chinese medicine / anticonvulsant / lithium agent), maternal ultrasound examination, high-intensity noise (> 80 db, ≥ 8 hours), extreme working conditions, weight, and thrombin time. Details of comparison of all maternal parameters between normal and abnormal fetal groups are displayed in Tables 1-5.

Multivariate regression analysis revealed that maternal age (OR = 1.039, 95% CI: 1.014-1.065, $p = 0.002$), gravid-

Table 2. — *Comparison of maternal and delivery history between normal and abnormal fetal groups.*

Parameters	Normal fetal group (n=5228)	Abnormal fetal group (n=145)	Total (n=5373)	t/χ^2	*p*
Gravidity					
Mean (SD)	1.77 (1.05)	2.34 (2.64)	1.79 (1.13)	-2.580	0.011
Parity					
Mean (SD)	0.26 (0.48)	0.32 (0.57)	0.26 (0.48)	-1.162	0.247
History of induced abortion, *n* (%)					
No	3785 (72.4)	87 (60.0)	3872 (72.1)	10.887	0.004
Yes	1441 (27.6)	58 (40.0)	1499 (27.9)		.
Unknown*	2 (0.0)	0 (0.0)	2 (0.0)		.
History of spontaneous abortion, *n* (%)					
No	4818 (92.2)	127 (87.6)	4945 (92.0)	4.362	0.113
Yes	405 (7.7)	18 (12.4)	423 (7.9)		.
Unknown*	5 (0.1)	0 (0.0)	5 (0.1)		.
History of threatened abortion, *n* (%)					
No	4989 (95.4)	134 (92.4)	5123 (95.3)	4.669	0.097
Yes	217 (4.2)	11 (7.6)	228 (4.2)		.
Unknown*	22 (0.4)	0 (0.0)	22 (0.4)		.
History of preterm birth, *n* (%)					
No	5193 (99.3)	145 (100.0)	5338 (99.3)	0.977	0.614
Yes	29 (0.6)	0 (0.0)	29 (0.5)		.
Unknown*	6 (0.1)	0 (0.0)	6 (0.1)		.
History of stillbirth, *n* (%)					
No	5094 (97.4)	140 (96.6)	5234 (97.4)	0.694	0.707
Yes	129 (2.5)	5 (3.4)	134 (2.5)		.
Unknown*	5 (0.1)	0 (0.0)	5 (0.1)		.

**Missing data are not included in statistical comparison between groups.*

Table 3. — *Comparison of maternal work environment between normal and abnormal fetal groups.*

Parameters	Normal fetal group (n=5236)	Abnormal fetal group (n=145)	Total (n=5381)	t/χ^2	*p*
Previous work in high-risk environments*, *n* (%)					
No	4758 (90.9)	118 (81.4)	4876 (90.7)	17 .163	<0.001
Yes	288 (5.5)	19 (13.1)	307 (5.7)		
Unknown**	190 (3.6)	8 (5.5)	195 (3.6)		
Contact with organic solvents, *n*(%)					
No	4800 (91.7)	123 (84.8)	4923 (91.5)	8.91	0.012
Yes	239 (4.6)	11 (7.6)	250 (4.6)		
Unknown**	197 (3.7)	11 (7.6)	207 (3.8)		

**High-risk work environment includes the workplace with high temperature, loud noises, dust, peculiar smell, and exposure to chemicals, heavy metals, and ionizing radiation. **Missing data are not included in statistical comparison between groups.*

ity (OR = 1.221, 95%: 1.107-1.348, $p < 0.0001$), passive smoking (OR = 1.763, 95% CI: 1.149-2.707, $p = 0.01$), maternal ultrasound examination (OR = 2.008, 95% CI: 1.210-3.333, $p = 0.007$), high-risk working condition (OR = 2.412, 95% CI: 1.278-4.552, $p = 0.007$), and thrombin time (OR = 0.895, 95% CI: 0.817-0.982, $p = 0.019$) were significantly associated with increased risk of congenital abnormality.

According to another univariate logistic regression analysis of 5,436 evaluable cases on paternal factors, the following factors were statistically associated with the congenital abnormality: paternal age, education level, high-risk workplace (printing industry, the footwear industry), alcohol consumption, high intensity noise (> 80 db, ≥ 8 hours), and heavy metal exposure. Details of comparison of all paternal parameters between normal and abnormal fetal groups are displayed in Tables 6 and the result of univariate analysis is presented in Table 7.

Multivariate regression analysis revealed that paternal age (OR= 1.022, 95% CI: 1.007-1.038, $p = 0.005$), higher education levels (junior high school: OR = 0.258, 95% CI: 0.124-0.537, $p = 0.000$, high school: OR = 0.231, 95% CI: 0.112-0.476, $p < 0.0001$, college: OR = 0.192, 95% CI: 0.088-0.415, $p < 0.0001$, and undergraduate: 0.152, 95% CI: 0.066-0.350, $p < 0.0001$), except for postgraduate education levels when compared to those with less than primary education, alcohol consumption (OR = 1.617, 95% CI: 1.072-2.440, $p = 0.022$) and heavy metal exposure (OR = 4.466, 95% CI: 1.556-12.818, $p = 0.005$) were significantly associated with increased risk of congenital abnormality.

According to another univariate logistic regression analysis of 5,381 evaluable cases for investigating the risk factors during pregnancy, extreme work environments such as

Table 4. — *Comparison of other maternal factors identified during pregnancy between normal and abnormal fetal groups.*

Parameters	*Normal fetal group (n=5232)*	*Abnormal fetal group (n=145)*	*Total (n=5377)*	t/χ^2	*p*
Exposure to the following drugs/substances					
Antibiotic, *n* (%)					
No	4978 (95.1)	142 (97.9)	5120 (95.2)	2.541	0.281
Yes	20 (0.4)	0 (0.0)	20 (0.4)		
Unknown	234 (4.5)	3 (2.1)	238 (4.4)		
Antipyretic analgesics, NSAID, *n* (%)					
No	4868 (93.0)	134 (92.4)	5002 (93.0)	0.611	0.737
Yes	193 (3.7)	7 (4.8)	200 (3.7)		
Unknown	171 (3.3)	4 (2.8)	175 (3.3)		
Tocolytic, *n* (%)					
No	4547 (86.9)	111 (76.6)	4658 (86.6)	16.938	<.001
Yes	482 (9.2)	28 (19.3)	510 (9.5)		
Unknown	203 (3.9)	6 (4.1)	209 (3.9)		
Anticancer drugs, *n* (%)					
No	5129 (98.0)	142 (97.9)	5271 (98.0)	0.102	0.950
Yes	3 (0.1)	0 (0.0)	3 (0.1)		
Unknown	100 (1.9)	3 (2.1)	103 (1.9)		
Vit A / vit A acid / vit A homolog, *n* (%)					
No	4915 (94.0)	132 (91.0)	5047 (93.9)	2.315	0.314
Yes	34 (0.7)	1 (0.7)	35 (0.7)		
Unknown	283 (5.4)	12 (8.3)	293 (5.5)		
Birth control pills					
No	4541 (86.8)	137 (94.5)	4678 (87.0)	7.377	0.007
Yes	691 (13.2)	8 (5.5)	699 (13.0)		.
Other drugs, *n* (%)					
No	4921 (94.0)	127 (87.6)	5048 (93.9)	18.051	<.001
Yes	117 (2.2)	11 (7.6)	128 (2.4)		
Unknown	194 (3.7)	7 (4.8)	202 (3.8)		
Supplementation					
Folic acid, *n* (%)					
No	612 (11.7)	27 (18.6)	639 (11.9)	6.464	0.011
Yes	4620 (88.3)	118 (81.4)	4739 (88.1)		.
Multivitamins, *n* (%)					
No	2201 (42.1)	69 (47.6)	2270 (42.2)	1.745	0.186
Yes	3028 (57.9)	76 (52.4)	3104 (57.8)		.
Unknown	3 (0.0)	0 (0.0)			
Other environmental exposure					
Exposure to toxic or harmful substances, *n* (%)					
No	5019 (95.9)	133 (91.7)	5153 (95.8)	6.225	0.013
Yes	213 (4.1)	12 (8.3)	225 (4.2)		.
X-ray irradiation, *n* (%)					
No	5033 (96.2)	141 (97.2)	5174 (96.2)	0.938	0.626
Yes	30 (0.6)	0 (0.0)	30 (0.6)		
Unknown	169 (3.2)	4 (2.8)	172 (3.2)		
B-mode USG examination, *n* (%)					
No	4448 (85.0)	110 (75.9)	4558 (84.8)	11.539	0.003
Yes	628 (12.0)	31 (21.4)	659 (12.3)		
Unknown	156 (3.0)	4 (2.8)	160 (3.0)		
Electromagnetic radiation, *n* (%)					
No	4774 (91.2)	130 (89.7)	4904 (91.2)	1.565	0.457
Yes	130 (2.5)	6 (4.1)	136(2.5)		
Unknown	328 (6.3)	9 (6.2)	337(6.3)		
Ionizing radiation, *n* (%)					
No	4972 (95.0)	138 (95.2)	5110 (95.1)	0.085	0.959
Yes	3 (0.1)	0 (0.0)	3 (0.1)		
Unknown	257 (4.9)	7 (4.8)	263 (4.9)		
High-intensity noise (> 80 db, ≥8 hours), *n* (%)					
No	4960 (94.8)	135 (93.1)	5095 (94.8)	6.512	0.039
Yes	26 (0.5)	3 (2.1)	29 (0.5)		
Unknown	246 (4.7)	7 (4.8)	253 (4.7)		

NSAID: non-steroidal anti-inflammatory drugs; USG: ultrasound; Vit: Vitamin.

Table 5. — *Comparison of vital signs and laboratory tests results during pregnancy between normal and abnormal fetal groups.*

Parameters	Normal fetal group (n=5236)	Abnormal fetal group (n=145)	Total (n=5381)	t/χ^2	*p*
Weight in kg, mean (SD)	55.36 (7.75)	56.43 (10.09)	55.39 (7.82)	-1.27	0.206
Blood pressure					
SBP, mmHg, mean (SD)	109.68 (9.59)	110.35 (12.09)	109.70 (9.66)	-0.664	0.508
DBP, mmHg, mean (SD)	67.57 (8.98)	67.99 (9.48)	67.58 (8.99)	-0.546	0.585
Renal function					
Blood sugar, mmol/L, mean (SD)	4.99 (3.94)	4.68 (0.78)	4.99 (3.89)	3.437	0.001
Creatinine, mmol/L, mean (SD)	48.44 (13.23)	48.18 (12.28)	48.44 (13.20)	0.207	0.836
Uric acid, mmol/L, mean (SD)	16.01 (11.92)	16.46 (11.63)	16.02 (11.92)	-0.382	0.703
Liver function					
ALT group, U/L, mean(SD)	23.11 (36.37)	23.93 (34.53)	23.14 (36.32)	-0.241	0.809
Hematology					
Hemoglobin, g/L	123.16 (39.23)	124.06 (51.42)	123.18 (39.56)	-0.195	0.846
RBC, 10^{12}/L	4.44 (3.86)	4.14 (0.90)	4.43 (3.82)	3.083	0.002
WBC, 10^{12}/L	8.59 (4.02)	8.67 (2.08)	8.59 (3.99)	-0.431	0.667
Triple prenatal screening					
Estriol level, nmol/24 h	2.38 (21.09)	1.24 (1.31)	2.35 (20.85)	3.187	0.001
Serum hCG level, IU/L	38.96 (142.48)	80.64 (323.07)	39.94 (149.31)	-1.274	0.206
AFP level, μg/L	59.33 (32.26)	58.58 (30.80)	59.32 (32.22)	0.229	0.819
Coagulation					
Activated partial thromboplastin time, s	28.54 (5.32)	28.56 (4.47)	28.54 (5.30)	-0.049	0.961
Plasma fibrinogen, g/L	3.58 (2.69)	3.39 (0.71)	3.58 (2.66)	2.247	0.026
Prothrombin time, s	12.06 (2.48)	12.16 (2.48)	12.06 (2.48)	-0.367	0.714
Thrombin time, s	17.20 (2.08)	16.78 (2.10)	17.19 (2.08)	1.944	0.052

AFP: alpha-fetoprotein; ALT: alanine aminotransferase DBP: diastolic blood pressure; hCG: human chorionic gonadotropin; RBC: red blood cell; SBP: systolic blood pressure; WBC: white blood cell.

high temperature workplace, solvent exposure, and RBC count were significantly associated with the occurrence of congenital abnormality. Details of comparison of other maternal factors during follow-up between normal and abnormal fetal groups are displayed in Tables 3 and 5 and the result of univariate analysis is presented in Table 7.

Multivariate regression analysis did not reveal any risk factor during pregnancy associated with congenital abnormality, but RBC count was revealed as a protective factor (OR = 0.349, 95% CI: 0.180-0.677, $p = 0.002$).

When maternal factors, paternal factors, and other factors identified from regular follow-up during pregnancy, a total of 5,261 evaluable cases were analyzed. Multivariate regression analysis revealed that maternal age (OR = 1.076, 95% CI: 1.007-1.148, $p = 0.029$), gravidity (OR = 1.153, 95% CI: 1.024-1.298, $p = 0.018$), and RBC count (OR = 0.374, 95% CI: 0.187-0.745, $p = 0.005$) measured during pregnancy follow-up were significantly associated with the occurrence of congenital abnormality after controlling other factors (Table 8).

Discussion

There are conflicting results on the association between mother's education level and congenital heart disease [17-19]. In the present study, there was a significant association between mother's education level and the occurrence of congenital anomaly ($p = 0.043$), and a trend of inverse correlation was observed. When compared to mothers who only received primary education using univariate logistic regression, those who had received undergraduate education were less likely to have a baby with congenital abnormality (OR= 0.248, 95% CI: 0.077-0.802), however, other levels of education were not considered relevant to the abnormal outcome. It was also confirmed from the multivariate regression analysis that mother's higher education levels was not a protective factor.

Other maternal factors such as mother's age, gravidity, passive smoking, maternal ultrasound examination, and high-risk working condition were identified as independent risk factors of congenital heart disease. Similar to other studies [20-23], mothers with older age, increased gravidity, passive smoking, and those working in high-risk condition were probably associated with the congenital defects. However, maternal ultrasound examination was considered as a risk factor of the congenital problem, whereas there is lack of evidence showing the association with maternal exposure to ionizing radiation or display terminals [24-26]. Evidence for the association of thrombin time and the abnormal outcome was not found in the literature as well. In agreement with suggestions by Liu *et al.* [27], the results might be biased and further study is warranted.

In this study, the relationship between paternal factors and the outcome of congenital heart defects were also explored. Similar to other large-scale studies [28-31], higher paternal age, lower education level, alcohol consumption, and heavy metal exposure were considered as possible risk factors of congenital anomaly. It further testifies that as for

Table 6. — *Comparison of paternal factors between normal and abnormal fetal groups.*

Parameters	Normal fetal group (n=5291)	Abnormal fetal group (n=145)	Total (n=5436)	t/χ^2	*p*
Age, years, mean (SD)	29.08 (6.60)	30.78 (6.52)	29.13 (6.61)	-3.025	0.002
Congenital heart disease, *n* (%)					
No	5201 (98.3)	144 (99.3)	5345 (98.3)	0.083	0.773
Yes	3 (0.1)	0 (0.0)	3 (0.1)		.
Unknown*	87 (1.6)	1 (0.7)	88 (1.6)		
Other disease(s), *n* (%)					
No	5009 (94.7)	137 (94.5)	5146 (94.7)	0.595	0.440
Yes	189 (3.6)	7 (4.8)	196 (3.6)		.
Unknown*	93 (1.8)	1 (0.7)	94 (1.7)		
Education level, *n* (%)					
Less than primary school	82 (1.5)	10 (6.9)	92 (1.7)	29.853	<0.001
Junior high school	1307 (24.7)	41 (28.3)	1348 (24.8)		.
Senior high school	1717 (32.5)	46 (31.7)	1763 (32.4)		.
College	1134 (21.4)	27 (18.6)	1161 (21.4)		.
Undergraduate	879 (16.6)	15 (10.3)	894 (16.4)		.
Postgraduate or above	79 (1.5)	4 (2.8)	83 (1.5)		.
Unknown*	93 (1.8)	2 (1.4)	95 (1.7)		
Occupation, *n* (%)					
Workman	1089 (20.6)	31 (21.4)	1120 (20.6)	3.328	0.853
Farmer	463 (8.8)	15 (10.3)	478 (8.8)		
Individual / private owners	970 (18.3)	26 (17.9)	996 (18.3)		
Civil servants or employees	504 (9.5)	12 (8.3)	516 (9.5)		
Housework	61 (1.2)	2 (1.4)	63 (1.2)		
Professional skill worker	982 (18.6)	21 (14.5)	1003 (18.5)		
Service or businessman	744 (14.1)	25 (17.2)	769 (14.1)		
Others	367 (6.9)	12 (8.3)	379 (7.0)		
Unknown*	111 (2.1)	1 (0.7)	112 (2.1)		
Previous work in high-risk environments**, *n* (%)					
No	4145 (78.3)	106 (73.1)	4251 (78.2)	4.451	0.108
Yes	816 (15.4)	32 (22.1)	848 (15.6)		
Unknown	330 (6.2)	7 (4.8)	337 (6.2)		
Smoking, *n* (%)					
No	3750 (70.9)	99 (68.8)	3849 (70.8)	0.774	0.379
Yes	1452 (27.4)	45 (31.3)	1497 (27.5)		
Unknown*	89 (1.7)	1 (0.7)	90 (1.7)		
Average daily smoking, number of cigarettes, mean (SD)	7.83 (5.69)	10.22 (8.69)	7.90 (5.82)	-1.839	0.073
Duration of smoking, years, mean (SD)	7.09 (5.12)	8.58 (6.35)	7.14 (5.16)	-1.552	0.128
Current smoker, *n* (%)					
No	243 (4.6)	6 (4.1)	249 (4.6)	0.396	0.529
Yes	1164 (22.0)	38 (26.2)	1202 (22.1)		
Unknown*	3884 (73.4)	101 (69.7)	3985 (73.3)		
Passive smoking, *n* (%)					
No	3050 (57.6)	82 (56.6)	3132 (57.6)	0.043	0.837
Yes	1031 (19.5)	29 (20.0)	1060 (19.5)		
Unknown*	1210 (22.9)	34 (23.4)	1244 (22.9)		
Current drinker, *n* (%)					
No	4457 (84.2)	112 (77.2)	4569 (84.1)	7.149	0.007
Yes	742 (14.0)	32 (22.1)	774 (14.2)		.
Unknown*	92 (1.7)	1 (0.7)	93 (1.7)		
Quit drinking, *n* (%)					
No	535 (72.1)	20 (62.5)	555 (71.7)	1.774	0.183
Yes	177 (23.9)	11 (34.4)	188 (24.3)		
Unknown*	30 (4.0)	1 (3.1)	31 (4.0)		
Average daily alcohol, liang, mean (SD)	1.61 (1.45)	1.43 (0.77)	1.60 (1.42)	1.147	0.258
Duration of drinking, years, mean (SD)	5.95 (5.72)	7.20 (5.43)	6.01 (5.71)	-1.17	0.242

Drug abuse addiction, *n* (%)					
No	5184 (98.0)	143 (98.6)	5327 (98.0)	0.904	0.342
Yes	14 (0.3)	1 (0.7)	15 (0.3)		
Unknown*	93(1.8)	1 (0.7)	94 (1.7)		
X-ray irradiation, *n* (%)					
No	5163 (97.6)	144 (100.0)	5307 (97.6)	1.004	0.605
Yes	17 (0.3)	0 (0.0)	17 (0.3)		
Unknown	111 (2.1)	1 (0.7)	112 (2.1)		
Electromagnetic radiation, *n* (%)					
No	4999 (94.5)	136 (93.8)	5135 (94.5)	1.345	0.510
Yes	162 (3.1)	6 (4.1)	168 (3.1)		
Unknown	130 (2.5)	3 (2.1)	133 (2.4)		
Ionizing radiation, *n*(%)					
No	5147 (97.3)	142 (97.9)	5289 (97.3)	1.981	0.371
Yes	20 (0.4)	0 (0.0)	20 (0.4)		
Unknown	124 (2.3)	3 (2.1)	127 (2.3)		
High-intensity noise (> 80 db, ≥8 hours), *n*(%)					
No	5011 (94.7)	133 (91.7)	514 4(94.6)	6.581	0.037
Yes	130 (2.5)	8 (5.5)	138 (2.5)		
Unknown	150 (2.8)	4 (2.8)	154 (2.8)		
Exposure to heavy metals (Pb, Hg, Cd, As, Cu, Mn), *n* (%)					
No	5123 (96.8)	138 (95.2)	5261 (96.8)	8.644	0.013
Yes	37 (0.7)	4 (2.8)	41 (0.8)		
Unknown	131 (2.5)	3 (2.1)	134 (2.5)		
Exposure to organic solvent, *n* (%)					
No	5126 (96.9)	140 (96.6)	5266 (96.9)	2.079	0.354
Yes	41 (0.8)	2 (1.4)	43 (0.8)		
Unknown	124(2.3)	3 (2.1)	127 (2.3)		
Exposure to pesticide, *n* (%)					
No	5163 (97.6)	143 (98.6)	5306 (97.6)	1.325	0.516
Yes	15 (0.3)	1 (0.7)	16 (0.3)		
Unknown	113 (2.1)	1 (0.7)	114 (2.1)		

*As: arsenic; Cd: cadmium; Cu: copper; Pb: lead; Hg: mercury; Mn: manganese. * Missing data are not included in statistical comparison between groups. **High-risk work industry include the followings: printing, footwear, electronics manufacturing, chemical, metal, furniture, rubber / plastic products, toy, pesticide, pulp mill, dyes and dyeing, refinery, tannery, and ceramics.*

the Chinese population, better health education and prevention of exposure to alcohol and heavy metal might be able to reduce the chance of congenital heart defects.

Together with maternal and paternal factors, as well as other factors identified during pregnancy follow-up, only two independent risk factors, higher maternal age, and increased gravidity, and one protective factor of higher RBC count measured during pregnancy follow-up were identified. Both maternal age and gravidity were discussed above and considered as known risk factors of congenital anomaly. Interestingly, in the present study, a significantly higher maternal RBC count observed in normal fetal group than abnormal fetal group ($4.44 \pm 3.86 \times 10^{12}$/L vs. $4.14 \pm 0.90 \times 10^{12}$/L, $p = 0.002$), was considered an independent protective factor (OR= 0.374, 95% CI: 0.187-0.745, $p = 0.005$). There is however not much evidence showing the relationship between RBC count and the abnormal outcome. Indeed, RBC itself may provide a storage reservoir of essential elements for fetal development such as folate, which was found closely related with the incidence of main birth defects including congenital heart defects [32]. Therefore, the maternal level of RBC-folate and its relationship with birth defects should be investigated in future studies.

One of the major limitation of the retrospective study was that the sample size was limited by the number of available medical records and unbalanced sample size included for analysis. It may bias the study results as discussed previously. A large-scale prospective study is recommended.

Conclusion

The retrospective analysis of maternal database in a single institution revealed that higher mother's age and increased gravidity might increase the risk, whereas the higher RBC count might reduce the chance of congenital heart diseases.

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Table 7. — *Univariate analyses of maternal factors, paternal factors, and other factors identified iuring pregnancy follow-up.*

Factors	*β*	*SE*	χ^2	*p*	*OR* (95%CI)
Maternal					
Age, years	0.027	0.009	8.361	0.004	1.027 (1.009-1.046)
Education level					
Less than primary school	(Control)				
Junior high school	-0.468	0.534	0.766	0.382	0.627 (0.220-1.786)
Senior high school	-0.823	0.539	2.335	0.127	0.439 (0.153-1.262)
College	-0.768	0.544	1.996	0.158	0.464 (0.160-1.346)
Undergraduate	-1.435	0.605	5.631	0.018	0.238 (0.073-0.779)
Postgraduate or above	-0.213	0.783	0.074	0.786	0.808 (0.174-3.750)
Occupation					
Workman	(Control)				
Farmer	-0.406	0.357	1.289	0.256	0.667 (0.331-1.343)
Individual/private owners	-0.157	0.303	0.267	0.605	0.855 (0.472-1.549)
Civil servants or employees	-0.381	0.370	1.058	0.304	0.683 (0.331-1.412)
Housework	-0.122	0.265	0.211	0.646	0.885 (0.527-1.488)
Professional skill worker	-1.388	0.536	6.716	0.010	0.250 (0.087-0.713)
Service or business people	-0.217	0.289	0.561	0.454	0.805 (0.457-1.419)
Others	-0.500	0.314	2.536	0.111	0.607 (0.328-1.122)
High-risk work in factories					
No	(Control)				
Yes	0.504	0.184	7.516	0.006	1.655 (1.154-2.372)
Unknown	-0.545	1.013	0.290	0.590	0.580 (0.080-4.217)
Passive smoking					
No	(Control)				
Yes	0.300	0.183	2.692	0.101	1.350 (0.943-1.933)
Alcohol drinking					
No	(Control)				
Yes	1.076	0.527	4.174	0.041	2.934 (1.045-8.240)
History of induced abortion					
No	(Control)				
Yes	0.550	0.176	9.727	0.002	1.733 (1.227-2.449)
Unknown	-8.861	551.800	0.000	0.987	0.000 (0.000-I)
History of spontaneous abortion					
No	(Control)				
Yes	0.441	0.271	2.643	0.104	1.554 (0.913-2.642)
Unknown	-10.003	406.900	0.001	0.980	0.000 (0.000-I)
History of threatened abortion					
No	(Control)				
Yes	0.586	0.336	3.042	0.081	1.796 (0.930-3.470)
Unknown	-12.015	539.700	0.001	0.982	0.000 (0.000-I)
Folic acid supplementation before or during pregnancy					
No	(Control)				
Yes	-0.516	0.225	5.244	0.022	0.597 (0.384-0.928)
Exposure to toxic or harmful substances before or during pregnancy					
No	(Control)				
Yes	0.798	0.310	6.617	0.010	2.222 (1.209-4.082)
Previous use of birth control pills					
No	(Control)				
Yes	-0.917	0.367	6.259	0.012	0.400 (0.195-0.820)
Previous use of tocolytic drugs					
No	(Control)				
Yes	0.809	0.224	13.053	0.000	2.246 (1.448-3.484)
Unknown	0.200	0.426	0.220	0.639	1.221 (0.530-2.813)
Previous intake of vitamin A / vitamin A acid / vitamin A homolog					
No	(Control)				
Yes	0.076	1.019	0.006	0.940	1.079 (0.147-7.945)
Unknown	0.307	0.334	0.843	0.359	1.359 (0.706-2.617)

Ultrasound examination					
No	(Control)				
Yes	0.694	0.212	10.771	0.001	2.002 (1.323-3.031)
Unknown	0.082	0.516	0.025	0.874	1.086 (0.395-2.986)
High-intensity noise (> 80 db, ≥ 8 hours)					
No	(Control)				
Yes	1.524	0.619	6.066	0.014	4.591 (1.365-15.441)
Unknown	0.073	0.394	0.034	0.853	1.076 (0.497-2.327)
Extreme work environment such as high temperature					
No (Control)					
Yes	0.975	0.261	13.929	0.000	2.652 (1.589-4.426)
Unknown	0.564	0.374	2.283	0.131	1.758 (0.846-3.656)
Gravidity	0.223	0.054	16.895	<.0001	1.249 (1.124-1.389)
Weight, kg	0.016	0.010	2.554	0.110	1.016 (0.996-1.036)
Thrombin time	-0.089	0.047	3.577	0.059	0.915 (0.834-1.003)
Paternal					
Age, years	0.024	0.008	9.314	0.002	1.025 (1.009-1.041)
Education level					
Less than primary school	(Control)				
Junior high school	-1.126	0.404	7.784	0.005	0.324 (0.147-0.715)
Senior high school	-1.314	0.401	10.770	0.001	0.269 (0.123-0.589)
College	-1.413	0.419	11.380	0.001	0.243 (0.107-0.553)
Undergraduate	-1.750	0.453	14.912	0.000	0.174 (0.071-0.422)
Postgraduate or above	-0.930	0.696	1.784	0.182	0.395 (0.101-1.544)
High-risk work in factories					
No	(Control)				
Yes	0.356	0.214	2.772	0.096	1.427 (0.939-2.169)
Unknown	0.006	0.425	0.000	0.989	1.006 (0.437-2.315)
Alcohol drinking					
No	(Control)				
Yes	0.506	0.210	5.790	0.016	1.658 (1.098-2.503)
High-intensity noise (> 80 db, ≥ 8 hours)					
No	(Control)				
Yes	0.880	0.376	5.489	0.019	2.411 (1.155-5.032)
Unknown	0.720	0.600	1.442	0.230	2.054 (0.634-6.654)
Heavy metal exposure					
No	(Control)				
Yes	1.444	0.535	7.278	0.007	4.235 (1.484-12.088)
Unknown	0.695	0.731	0.903	0.342	2.003 (0.478-8.398)
Factors during pregnancy follow-up					
RBC count	-0.970	0.336	8.348	0.004	0.379 (0.196-0.732)
Solvent exposure					
No	(Control)				
Yes	1.285	0.477	7.260	0.007	3.614 (1.419-9.204)
Unknown	-0.090	0.591	0.023	0.879	0.914 (0.287-2.911)
Extreme work environment such as high temperature					
No	(Control)				
Yes	1.164	0.435	7.174	0.007	3.203 (1.367-7.508)
Unknown	0.298	0.517	0.332	0.565	1.346 (0.489-3.707)

Table 8. — *Multivariate analysis of maternal factors, paternal factors, and other factors identified during pregnancy follow-up.*

Factors	*β*	*SE*	χ^2	*p OR* (95%CI)	
Maternal age, years	0.073	0.033	4.764	0.029	1.076 (1.007-1.148)
Gravidity	0.142	0.060	5.555	0.018	1.153 (1.024-1.298)
RBC count, 10^{12}/L	-0.984	0.352	7.809	0.005	0.374 (0.187-0.745)

OR = odds ratio; RBC = red blood cell; SE = standard of error.

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