ORIGINAL RESEARCH

The Relationship Between Congenital Heart Disease in Newborns and Maternal Prenatal Folic Acid Supplementation, and Analysis of Other High-Risk Factors

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ABSTRACT

Objective • To analyze the relationship between congenital heart disease (CHD) in newborns and maternal prenatal folic acid supplementation, as well as other high-risk factors.

Method • A retrospective analysis was conducted on clinical data of 114 pregnant women diagnosed with congenital heart disease (CHD) in the prenatal stage at our hospital between January 2021 and January 2023. These pregnant women were included in the case group. Additionally, an equal number of pregnant women with normal examination results during the same period were selected as the control group at a 1:1 ratio. Basic information about the families of pregnant women and information about relevant exposure factors during the periconception period were analyzed based on survey forms previously completed by pregnant women during their prenatal check-ups at the hospital. Possible influencing factors were analyzed through multifactor logistic regression.

Results • High-risk factors during the perinatal period for new CHD in newborns include maternal age at this pregnancy >35 years (OR=1.907), the presence of adverse pregnancy history (OR=2.213), a family history of CHD (OR=3.049), exposure to secondhand smoke during the perinatal period (OR=2.934), the use of cold medications (OR=1.719), fever (OR=2.034), exposure to noisy environments (OR=1.981), prolonged use of electronic devices (OR=1.827), consumption of pickled foods (OR=1.892). Prenatal folic acid supplementation is a protective factor for new CHD in newborns (OR=0.342).

Conclusion • Pregnant women should choose an appropriate gestational age for conception. During the perinatal period, pregnant women should avoid exposure to the aforementioned high-risk factors as much as possible and supplement folic acid appropriately. It is essential to cultivate good dietary and lifestyle habits, as this has significant implications for preventing and reducing the occurrence of CHD in newborns. Healthcare professionals should prioritize educating pregnant women about the risks associated with the identified high-risk factors and emphasize the importance of early prenatal care. Furthermore, promoting appropriate folic acid supplementation during the periconception period should be an integral part of prenatal care protocols. By implementing these recommendations, healthcare providers can contribute to reducing the occurrence of CHD in newborns and improving maternal and infant health outcomes. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Congenital heart disease (CHD) in newborns is a group of various heart structural abnormalities that begin forming during the early stages of embryonic development.[1] Congenital heart disease (CHD) is a significant global health concern, with a substantial impact on morbidity and mortality. It is one of the most common types of congenital anomalies, affecting a considerable number of newborns worldwide. The incidence rate of CHD varies across populations, but it is estimated to occur in approximately 8 out of every 1,000 live births, making it a prevalent condition that warrants attention. The pathogenesis of CHD involves a complex interplay between genetic and environmental factors. While certain genetic factors contribute to CHD development, environmental exposures have also been implicated as important risk factors. Studies have shown that specific environmental factors, such as maternal exposure to tobacco smoke, certain medications, and certain occupational hazards, can increase the risk of CHD in offspring.

These abnormalities include ventricular septal defects and atrial septal defects, among others, which can pose

significant psychological and physiological challenges for affected infants and their families.[2] Newborn CHD is one of the most common severe diseases during the neonatal period, often requiring early intervention and treatment to safeguard the infant's life and health. The pathogenesis of CHD is complex, resulting from interactions between genetic and environmental factors.[3] While some CHD cases can be traced back to familial genetics, environmental factors also play a critical role in the occurrence of CHD. The periconception period is a crucial phase for fetal growth and development, making the health of both the mother and the infant and their exposure to various factors during this period significantly influence the risk of CHD.[4]

Folate, a B vitamin, has been widely studied and recognized for its importance during the periconception period.[5] Folate plays a vital role in DNA synthesis and cell division, particularly during the development of the embryonic neural tube and cardiovascular system.[6] It also plays a crucial role in embryonic development and has been extensively studied in relation to CHD. Beyond its general importance in DNA synthesis and cell division, folate deficiency has been associated with an increased risk of CHD. The biological mechanisms underlying this relationship involve the disruption of normal embryonic development, particularly in the formation of the heart and blood vessels.[7]

Despite the existing body of research, gaps still remain in our understanding of the relationship between folate intake and CHD. Previous studies have yielded conflicting findings, and further research is needed to elucidate the precise role of folate in CHD prevention. By addressing these gaps, we aim to contribute to the existing knowledge and provide a clearer understanding of the impact of folate intake on CHD risk.

Therefore, the specific aim of this study is to analyze the relationship between maternal prenatal folic acid supplementation and the risk of CHD in newborns, taking into account other high-risk factors. Based on preliminary data and existing literature, we hypothesize that higher periconceptional folate intake will be associated with a lower risk of CHD in newborns.

OBJECTIVES AND METHODS

Study Subjects

A retrospective analysis was conducted on clinical data of 114 pregnant women diagnosed with CHD in newborns in our hospital from January 2021 to January 2023, and they were included in the case group.

The inclusion criteria for the case group were as follows: (1) Gestational age > 14 weeks and diagnosis of CHD through fetal system ultrasound examination and FECG performed by specialist physicians; This criterion was selected to ensure that participants had reached a stage in pregnancy where comprehensive fetal cardiac examinations could be conducted. Early in pregnancy, ultrasound examinations may not provide a complete assessment of fetal cardiac structures. By including participants with a gestational age of >14 weeks, the study aimed to enhance the accuracy and reliability of CHD diagnosis, as well as to capture a representative sample of individuals with confirmed CHD. (2) Absence of mental or consciousness abnormalities in pregnant women, emotional stability, and willingness to cooperate with the investigation; (3) Confirmation through follow-up after induction or delivery; (4) Absence of other fetal abnormalities, genetic diseases, chromosomal abnormalities, etc.; (5) Exclusion of those lost to follow-up and those with incomplete investigation results. An equal number of pregnant women with normal examination results during the same period were selected as the control group in a 1:1 ratio.

The inclusion criteria for the control group were as follows: (1) Pregnant women with no abnormalities in fetal system ultrasound examination and FECG; (2) Pregnant women with a similar examination time and gestational age to the case group; (3) Absence of mental or consciousness abnormalities in pregnant women, emotional stability, and willingness to cooperate with the investigation; (4) No postpartum abnormalities upon follow-up; (5) Absence of other systemic abnormalities, genetic diseases, chromosomal abnormalities, etc.; (6) Exclusion of those lost to follow-up and those with incomplete investigation results.

In addition to matching on examination results, other key criteria were utilized to select the control group. These criteria included age and gestational age. Matching on age helps to control for potential age-related factors that may influence the risk of CHD. By ensuring that the distribution of age is similar between the case and control groups, the study aims to minimize the confounding effect of age on the relationship between the exposure of interest (e.g., folic acid supplementation) and CHD risk.

Methods

Both groups of study subjects are pregnant women who have undergone antenatal examinations at the hospital and have completed the questionnaire. The survey focuses on factors related to the periconception period, mainly comprising basic information and exposure to periconception environmental factors. (1) Basic information includes newborn gender, gestational age at birth, mother's age during the current pregnancy, gravidity, parity, history of adverse pregnancies, maternal educational level, paternal educational level, family's average monthly income per capita, and CHD family history. (2) Exposure to environmental factors during the periconception period includes smoking, exposure to secondhand smoke, alcohol consumption, use of cold medications, fever, contact with pets, exposure to radioactive materials, exposure to biochemical substances, exposure to noisy environments, proximity to substations in the residential area, proximity to polluting industries, folic acid supplementation, calcium supplementation, prolonged daily use of electronic devices (more than 4 hours), and consumption of pickled foods, among others.

The selection of survey factors was guided by a comprehensive review of the existing literature on CHD and its potential risk factors. Factors that have consistently

demonstrated significant associations with CHD in previous studies were included to ensure that the survey captured important variables known to be related to CHD risk. Additionally, factors with theoretical relevance to CHD development were also considered to explore potential novel associations or further validate existing evidence.

Exposure assessment for environmental factors typically involved collecting information on the frequency, duration, and intensity of exposure. For example, if the environmental factor under investigation was maternal smoking during pregnancy, participants were asked to provide information on the number of cigarettes smoked per day, the duration of smoking during pregnancy, and any passive exposure to smoke in the household.

Other environmental factors, such as maternal occupational exposures or medication use, were assessed using similar approaches, collecting information on the duration and intensity of exposure. In some cases, validated questionnaires or standardized measures were utilized to assess exposure levels.

Quality Control

To ensure the quality of the questionnaire, surveyors received training before conducting the surveys. After each survey, they conducted face-to-face questionnaire surveys with the subjects and checked for any missing information. Auditors immediately collected and reviewed the questionnaires to minimize omissions and reporting errors.

The auditors responsible for data review underwent rigorous training to familiarize themselves with the study's objectives, survey instruments, and data collection procedures. They were trained to meticulously examine the questionnaire data for completeness, consistency, and accuracy. During the review process, auditors carefully checked each questionnaire for missing responses, ensuring that all relevant questions were answered. They also cross-checked responses for internal consistency, identifying any discrepancies or illogical patterns that may indicate data entry errors or participant misunderstandings. To verify the accuracy of the questionnaire data, auditors conducted data validation procedures. This involved comparing the responses provided by participants to the original survey instrument and verifying that the data entered into the database accurately reflected the participants' intended responses. Any inconsistencies or discrepancies were thoroughly investigated and resolved through consultation with the research team and, if necessary, by reaching out to participants for clarification. The auditors also played a crucial role in maintaining data integrity during the data entry process. They performed regular checks to identify and correct any errors or discrepancies in the entered data, ensuring that the final dataset was as accurate and reliable as possible.

Statistical Analysis

A database was established using Epi Data 3.1 software, and data analysis was performed using SPSS 22.0 software. For continuous data, mean and standard deviation were used to describe the distribution, and statistical analysis was conducted using methods such as *t* tests or analysis of variance. For categorical data, frequency and percentage were used to describe the distribution, and statistical analysis was carried out using methods like chi-square tests or Fisher's exact tests. Non-parametric tests were used for ordinal data. Multifactorial conditional logistic regression analysis was employed to determine the factors influencing the occurrence of CHD in newborns. A significance level of $P < .05$ was considered statistically significant.

For skewed data distributions, logarithmic transformations were applied to normalize the data before analysis. Outliers were identified using calculation of z-scores, and their impact on the analysis was assessed using sensitivity analyses. Missing data were handled using multiple imputation. Sensitivity analyses were conducted to assess the robustness of the findings under different missing data assumptions. In the multifactorial conditional logistic regression analysis, testing for potential interaction terms to assess effect modification were explored to identify the most appropriate model. Interaction terms were constructed based on theoretical considerations. These interactions were included in the models to evaluate if the association between the exposure of interest and CHD risk varied by other factors included in the analysis. The analysis accounted for potential confounders identified during the matching process and in the initial analysis phases. These confounders were adjusted for in the regression models to control for their influence on the association between the exposure of interest (e.g., folic acid supplementation), high-risk factors, and CHD risk. The specific confounders adjusted for were determined based on prior knowledge, theoretical considerations, and statistical significance. Adjustments were made by including these confounders as covariates in the regression models, allowing for a more accurate estimation of the association of interest.

RESULTS

Comparison of Basic Information

A comparison was made between the two groups of study subjects based on their basic information. Statistically significant differences were observed in the distribution of maternal age at this pregnancy, adverse pregnancy history, and family history of congenital CHD ($P < .05$). Please refer to Table 1.

Comparison of Maternal Prenatal Environmental Exposure Factors

A comparison was made between the two groups of study subjects regarding maternal prenatal environmental exposure factors. Statistically significant differences were observed in the distribution of exposure to secondhand smoke, use of cold medications, contact with pets, fever, exposure to noisy environments, folic acid supplementation, prolonged use of electronic devices, and consumption of pickled foods ($P < .05$). Please refer to Table 2.

Table 1. Comparison of Basic Information

	Case (n=114)	Control (n=114)	t/χ^2	*P* value
Newborn Gender			0.017	.894
Male	55 (48.25%)	56 (49.12%)		
Female	59 (51.75%)	58 (50.88%)		
Birth Month			0.743	.388
Full-term	96 (84.21%)	91 (79.82%)		
Preterm or >2 weeks overdue	18 (15.79%)	23 (20.18%)		
Maternal Age at This Pregnancy (years)			3.921	.047
>35	29 (25.44%)	17 (14.91%)		
≤35	85 (74.56%)	97 (85.09%)		
Parity (times)	1.86±0.72	1.79±0.67	0.759	.448
Gravidity (times)	1.37±0.38	1.42±0.34	1.047	.296
Adverse Pregnancy History			7.745	.005
Yes	32 (28.07%)	15 (13.16%)		
No	82 (71.93%)	99 (86.84%)		
Maternal Education Level			0.289	.590
High school or below	69 (60.53%)	65 (57.02%)		
College and above	45 (39.47%)	49 (42.98%)		
Paternal Education Level			0.282	.595
High school or below	55 (48.25%)	51 (44.74%)		
College and above	59 (51.75%)	63 (55.26%)		
CHD Family History			6.947	.008
Yes	15 (13.16%)	4 (3.51%)		
No	99 (86.84%)	110 (96.49%)		
Family Average Monthly Income			0.336	.562
≤5000	100 (87.72%)	97 (85.09%)		
>5000	14 (12.28%)	17 (14.91%)		

Table 2. Comparison of Maternal Prenatal Environmental Exposure Factors

Variable	Case (n=114)	Control (n=114)	χ^2	*P* value
Smoking	7 (6.14%)	3 (2.63%)	1.673	.195
Secondhand Smoke	50 (43.86%)	22 (19.30%)	15.914	<.001
Alcohol Consumption	34 (29.82%)	29 (25.44%)	0.548	.459
Cold Medication Use	48 (42.11%)	32 (28.07%)	4.929	.026
Fever	40 (35.09%)	23 (20.18%)	6.338	.011
Contact with Pets	50 (43.86%)	34 (29.82%)	4.825	.028
Contact with Radioactive Substances	12 (10.53%)	8 (7.02%)	0.876	.349
Contact with Biochemical Substances	11 (9.65%)	8 (7.02%)	0.516	.472
Exposure to Noisy Environments	29 (25.44%)	16 (14.04%)	4.679	.030
Presence of Substation Around Residence	14 (12.28%)	11 (9.65%)	0.404	.524
Presence of Polluting Enterprises Around Residence	17 (14.91%)	16 (14.04%)	0.035	.850
Folic Acid Supplementation	85 (74.56%)	104 (91.23%)	11.166	<.001
Calcium Supplementation	73 (64.04%)	80 (70.18%)	0.973	.323
Prolonged Use of Electronic Devices	62 (54.39%)	44 (38.60%)	5.712	.016
Consumption of Pickled Foods	35 (30.70%)	21 (18.42%)	4.639	.031

Table 3. Variable Assignments

Variable	Assignment
Newborns with CHD	No=0, Yes=1
Maternal Age	≤35=0, >35=1
Adverse Pregnancy History	No=0, Yes=1
Family History of CHD	No=0, Yes=1
Exposure to Secondhand Smoke	No=0, Yes=1
Use of Cold Medications	No=0, Yes=1
Fever	No=0, Yes=1
Contact with Pets	No=0, Yes=1
Exposure to Noisy Environments	No=0, Yes=1
Use of Folic Acid	No=0, Yes=1
Prolonged Use of Electronic Devices	No=0, Yes=1
Consumption of Pickled Foods	No=0, Yes=1

Table 4. Multifactorial Logistic Regression Analysis of Newborns with CHD

Factor	B	SB	Wald χ^2	*P* value	OR (95%CI)
Maternal Age >35 years	0.647	0.281	5.062	.022	1.907 (1.074-3.352)
Adverse Pregnancy History	0.797	0.361	4.815	.026	2.213 (1.082-4.499)
Family History of CHD	1.109	0.493	5.164	.025	3.049 (1.162-7.989)
Exposure to Secondhand Smoke	1.073	0.306	12.427	<.001	2.934 (1.615-5.332)
Use of Cold Medications	0.543	0.259	4.521	.036	1.719 (1.039-2.832)
Fever	0.713	0.298	5.788	.015	2.034 (1.141-3.647)
Contact with Pets	0.476	0.257	3.548	.062	1.613 (0.985-2.634)
Exposure to Noisy Environments	0.683	0.311	4.892	.029	1.981 (1.083-3.619)
Use of Folic Acid	-1.085	0.359	9.217	.001	0.342 (0.167-0.685)
Prolonged Use of Electronic Devices	0.593	0.248	5.846	.013	1.827 (1.116-2.943)
Consumption of Pickled Foods	0.638	0.297	4.685	.032	1.892 (1.061-3.364)

Multifactorial Logistic Regression Analysis of Newborns with CHD

A logistic regression model was constructed with the occurrence of CHD in newborns as the dependent variable. The independent variables with statistically significant results from the aforementioned univariate analysis were included in the model (variable assignments are detailed in Table 3). High-risk factors for CHD during the prenatal period include maternal age >35 years (OR=1.907), a history of adverse pregnancies (OR=2.213), a family history of CHD (OR=3.049), exposure to secondhand smoke during pregnancy (OR=2.934), the use of cold medications (OR=1.719), fever (OR=2.034), exposure to noisy environments (OR=1.981), prolonged use of electronic devices (OR=1.827), and consumption of pickled foods (OR=1.892). In contrast, the prenatal use of folic acid is a protective factor against CHD (OR=0.342). Please refer to Table 4 for details.

DISCUSSION

In recent years, the incidence of congenital heart disease (CHD) in newborns in China has shown a gradually increasing trend, yet the clinical mechanisms behind the disease remain incompletely understood.[8] Several studies[9-11] propose a close relationship between the occurrence of newborn CHD and genetic and environmental factors, as well astheir interaction. While genetic factors are challenging to alter and prevent, environmental factors are relatively controllable. Hence, early detection and identification of environmental risk factors associated with newborn CHD during pregnancy hold significant preventive implications. The results of this study indicate that high-risk factors during the prenatal period for newborn CHD include maternal age >35 years (OR=1.907), a history of adverse pregnancies (OR=2.213), a family history of CHD (OR=3.049), exposure to secondhand smoke during pregnancy (OR=2.934), the use of cold medications (OR=1.719), fever (OR=2.034), exposure to noisy environments (OR=1.981), prolonged use of electronic devices (OR=1.827), and consumption of pickled foods (OR=1.892), while the use of folic acid during pregnancy serves as a protective factor against newborn CHD (OR=0.342).

This study found that maternal age >35 years significantly elevates the risk of newborn CHD, in line with previous research.[12] Advanced maternal age might lead to abnormal egg cell division and fetal congenital malformations, thereby increasing the risk of right ventricular outflow tract obstruction, tricuspid valve atresia, and transposition of the great arteries.[13] Other studies[14] suggest that newborns with a family history of CHD have a significantly higher risk of CHD compared to those without such a history, which aligns with the results of this study, indicating a certain genetic basis for CHD. Former research[15] has confirmed that both active and passive smoking can impact the incidence of various diseases. In China, the rate of active female smoking is relatively low, but passive smoking is higher. Studies[16]

indicate that active and passive smoking can increase the risk of newborns developing CHD. The potential reasons could be the impact of nicotine and carbon monoxide produced after tobacco combustion, leading to embryonic ischemia and hypoxia, resulting in malformations. However, due to the limited number of smoking samples in this study, smoking did not emerge as a risk factor for newborn CHD in the statistical analysis. The use of medications during pregnancy is among the key reasons for congenital cardiovascular disease. Overseas literature[17] confirms that fever during critical periods of fetal development can cause cardiac malformations, and the use of antibiotics and antipyretic analgesics after a fever increases the risk of CHD. Additionally, this study found that exposure to noisy environments might be a risk factor for newborn CHD. The reasons could be related to the physical stress experienced by pregnant women due to exposure to noise, radiation, or vibration, causing adverse reactions like headaches, insomnia, and irritability. These reactions might affect normal fetal development, increasing the occurrence of CHD.

Research[18] has shown that consuming pickled foods during pregnancy may be a risk factor for newborns developing CHD. This may be related to a large amount of nitrite and its derivatives in pickled foods. Nitrites can react with protein degradation products in pickled products to form nitrosamines, powerful carcinogens. Studies[19] indicate that nitrites can enter the fetal body through the placenta, and infants under six months are susceptible to nitrites. The relative risk of brain cancer in children under five is related to the maternal intake of nitrites through food. Scholars such as Mijatovic-Vukas[20] have demonstrated that a maternal diet rich in vegetables, fruits, high-quality proteins, and seafood during pregnancy may help reduce the risk of ventricular septal defect in newborns. This study found that pregnant women who use electronic devices for extended periods daily (>4 hours) may be at risk of having newborns with CHD. This might be associated with pregnant women spending long periods sitting and engaging in activities like watching television, playing games, shopping on their phones, and watching videos. Experimental research[21] has confirmed that prolonged sedentary behavior can lead to adverse cardiovascular metabolic effects. On the other hand, as for protective factors, the results of this study show that taking folic acid during pregnancy is a protective factor against newborn CHD. Previous research[22] has indicated that folic acid supplementation in pregnant women can effectively prevent fetal neural tube defects. Another case-control study[23] in different populations suggests that supplementing folic acid and other vitamins can reduce the incidence of newborn CHD. The results of this study are consistent with previous related research.

Understanding the possible mechanisms can provide insights into, CHD's etiology and suggest potential preventive and intervention strategies.

Firstly, the finding that prenatal folic acid supplementation is a protective factor for CHD in newborns is biologically plausible and supported by existing literature. Folate, a B vitamin, plays a crucial role in DNA synthesis and cell division during embryonic development, particularly in the formation of the neural tube and cardiovascular system. Folate deficiency has been associated with an increased risk of neural tube defects and has also been implicated in the development of structural heart abnormalities, including CHD. Several studies have demonstrated that adequate folic acid intake during the periconception period can reduce the risk of CHD. The protective effect of folic acid supplementation on CHD occurrence could be attributed to its role in supporting proper embryonic development and preventing developmental abnormalities.

Secondly, the identified high-risk factors for CHD in newborns, such as maternal age, adverse pregnancy history, family history of CHD, exposure to secondhand smoke, use of cold medications, fever, exposure to noisy environments, prolonged use of electronic devices, and consumption of pickled foods, also have biological plausibility and are consistent with previous research.

Thirdly, oxidative stress has been implicated in the pathogenesis of CHD. Increased production of reactive oxygen species (ROS) and inadequate antioxidant defense mechanisms can lead to oxidative damage to cellular components, including lipids, proteins, and DNA. This oxidative damage can contribute to the development and progression of atherosclerosis, a key underlying mechanism in CHD. Exploring the sources of ROS generation, the interplay between oxidative stress and endothelial dysfunction, and the impact on lipid metabolism and plaque formation would provide a more mechanistic understanding of how oxidative stress contributes to CHD.

Inflammation is another crucial process in CHD development. Chronic low-grade inflammation, characterized by increased levels of pro-inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), has been associated with an increased risk of CHD. Inflammatory processes contribute to endothelial dysfunction, promote atherosclerotic plaque formation, and can trigger plaque rupture and thrombosis. Examining the mechanisms by which inflammation influences these processes, the interplay between immune cells, endothelial cells, and smooth muscle cells, and the role of specific inflammatory pathways would enhance our understanding of the inflammatory mechanisms underlying CHD.

Advanced maternal age (>35 years) has been associated with an increased risk of CHD, which may be attributed to the age-related decline in oocyte quality and increased chromosomal abnormalities. Adverse pregnancy history, such as previous miscarriages or stillbirths, can indicate underlying genetic or environmental factors that contribute to the risk of CHD. A family history of CHD suggests a genetic predisposition to the condition, as certain genetic variants have been linked to an increased risk of CHD.

Exposure to secondhand smoke, as well as the use of cold medications, fever, and exposure to noisy environments,

can lead to oxidative stress and inflammation, which may disrupt normal cardiac development and increase the risk of CHD. Prolonged use of electronic devices, which emit electromagnetic radiation, and consumption of pickled foods, which may contain nitrates and nitrites, have been hypothesized to have potentially detrimental effects on fetal development, including the cardiovascular system.

Based on the findings of the study, the specific recommendations for pregnant women to minimize their risk of having a child with congenital heart disease (CHD) include:

Avoid exposure to secondhand smoke: Pregnant women should avoid exposure to secondhand smoke as much as possible. Secondhand smoke has been associated with an increased risk of CHD in infants. If you live with a smoker, encourage them to quit or smoke outside the house to minimize exposure. Additionally, try to avoid environments where smoking is prevalent, such as bars or events with heavy smoking.

Limit the use of certain medications: Some medications have been linked to an increased risk of CHD in infants. It is important to consult with your healthcare provider before taking any medications during pregnancy. Provide a detailed list of all the medications you are currently taking or planning to take, including prescription drugs, over-the-counter medications, and herbal supplements. Your healthcare provider can assess the potential risks and benefits and recommend safer alternatives if necessary.

Folic acid supplementation: Folic acid is a B vitamin that plays a crucial role in fetal development, including the formation of the baby's heart. Taking folic acid before and during early pregnancy can significantly reduce the risk of CHD. It is recommended that all women of childbearing age take a daily folic acid supplement of 400-800 micrograms (mcg) to ensure adequate levels before conception and during the early stages of pregnancy. Your healthcare provider can provide you with specific recommendations on the appropriate dosage.

Maintain a healthy lifestyle: Adopting a healthy lifestyle during pregnancy can help minimize the risk of CHD. This includes eating a balanced diet rich in fruits, vegetables, whole grains, and lean proteins. Regular physical activity, as recommended by your healthcare provider, can also contribute to overall health and reduce the risk of complications. Avoiding excessive alcohol consumption and illicit drug use is crucial, as these substances can increase the risk of CHD and other adverse outcomes.

Attend prenatal care visits: Regular prenatal care is essential for monitoring the health of both the mother and the developing baby. Attend all scheduled prenatal care visits and follow the recommendations provided by your healthcare provider. These visits allow for the identification and management of any potential risk factors or complications that may contribute to the development of CHD.

The findings of the study have important implications for both clinical practice and public health, particularly in the context of prenatal care programs and public awareness campaigns. 1) Identifying high-risk pregnant women: The study's findings can contribute to the development of screening strategies to identify high-risk pregnant women who may benefit from targeted interventions to reduce the risk of CHD in their offspring. Screening tools can be developed based on the identified risk factors, such as maternal smoking, medication use, and inadequate folic acid intake. Implementing these screening tools as part of routine prenatal care can help identify women who require additional support and interventions. 2) Targeted interventions and lifestyle modifications: High-risk pregnant women identified through screening can be offered targeted interventions to minimize the risk of CHD in their offspring. This may involve providing personalized counseling and support for lifestyle modifications, such as smoking cessation programs, guidance on maintaining a healthy diet, and encouraging regular physical activity during pregnancy. Additionally, emphasizing the importance of folic acid supplementation according to established guidelines can help reduce the risk of CHD. 3) Integration into prenatal care programs: The findings can be integrated into existing prenatal care programs to enhance their effectiveness in preventing CHD. Healthcare providers can be trained to identify and address modifiable risk factors during prenatal visits. Educational materials and resources can be developed to provide evidence-based information to pregnant women about the importance of healthy lifestyle choices and folic acid supplementation. Integration of these strategies within prenatal care programs can help optimize maternal and fetal health outcomes. 4) Public health campaigns: Public health campaigns can play a vital role in raising awareness about modifiable risk factors for CHD among the general population. These campaigns can utilize various channels, such as mass media, social media platforms, and community outreach programs, to disseminate information about the impact of maternal smoking, medication use, and folic acid intake on the risk of CHD in infants. The campaigns can also emphasize the importance of preconception care and encourage women of childbearing age to adopt healthy behaviors and optimize their health before pregnancy. 5) Collaborative efforts: Collaboration among healthcare providers, public health professionals, and policymakers is crucial in implementing these recommendations. Healthcare systems can establish guidelines and protocols to ensure the consistent identification and management of high-risk pregnant women in clinical settings. Public health agencies can allocate resources and support the development and dissemination of educational materials. Policymakers can advocate for policies that promote healthy behaviors and improve access to prenatal care services. 6) The findings of this study have broader implications in the field of developmental origins of health and disease (DOHaD). This underscores the importance of prenatal and early-life interventions in preventing not only CHD but also other chronic diseases. By identifying and addressing modifiable

risk factors during pregnancy, we have the potential to improve long-term cardiovascular health outcomes for both the mother and the child. Further research in the DOHaD field can explore the underlying mechanisms linking early-life exposures to cardiovascular health outcomes. This can involve investigating epigenetic modifications, developmental programming, and gene-environment interactions.

CONCLUSION

Congenital heart disease (CHD) poses a significant threat to the health and lives of newborns, resulting in a substantial disease burden. Investigating the etiology of this condition is of great significance, and research on environmental risk factors can provide robust scientific evidence for the primary prevention of newborn CHD. Preconception couples should receive comprehensive health education. Pregnant women should choose an appropriate age for conception, avoid contact with the high-risk factors mentioned during the periconception period, and supplement folic acid appropriately. Developing good dietary and lifestyle habits is highly significant for preventing and reducing the occurrence of newborn CHD.

It should be noted that although this study provides valuable information regarding the relationship between newborn CHD and maternal periconceptional folic acid intake and other high-risk factors, it has some limitations. Firstly, the study design is retrospective and conducted at a single center. This design introduces inherent limitations, such as potential selection bias and the inability to establish a cause-and-effect relationship. The findings may not be generalizable to the broader population, as they may be influenced by specific characteristics of the study population or the healthcare practices at the particular hospital where the study was conducted. Secondly, the study relies on self-reported survey forms completed by pregnant women during their prenatal check-ups. This introduces the possibility of recall bias, as participants may not accurately remember or report their exposure to certain factors during the periconception period.

Additionally, the accuracy of the reported information depends on the participants' understanding and interpretation of the questions, which may vary. Furthermore, there may be potential confounding factors not adequately accounted for in the analysis. Although multifactor logistic regression was employed to analyze possible influencing factors, there is still a possibility of residual confounding, which could affect the observed associations between prenatal folic acid supplementation, high-risk factors, and the occurrence of CHD in newborns. Unmeasured or unknown confounders could have influenced the results.

Acknowledging and discussing the limitations of the study is crucial for providing a comprehensive and balanced view of the research. Addressing them here will further enhance the interpretation of the results and provide insights into areas that require further investigation. Specifically, the following limitations are discussed:

Retrospective design and inherent biases: The retrospective design of the study introduces certain limitations and potential biases. Recall bias, where participants may have difficulty accurately recalling past exposures or events, is a concern in retrospective studies. Additionally, selection bias may arise from the non-random selection of participants or the reliance on existing medical records. Discussing these biases will emphasize the need for caution when interpreting the results and highlight the potential impact on the validity and generalizability of the findings.

Sample size and generalizability: The study's sample size can influence the generalizability of the findings. If the sample size is small, the study may not have had sufficient statistical power to detect small or moderate effects. This limitation should be explicitly addressed, and its potential implications for the generalizability of the findings to larger populations should be discussed. Future research with larger sample sizes would be valuable to validate and strengthen the current findings.

Potential confounding factors: Despite efforts to control for confounding factors in the analysis, it is possible that some important confounders were not fully accounted for. Unmeasured or residual confounding can impact the observed associations between the exposure variables and CHD outcomes. Discussing the potential confounding factors not controlled for will highlight the limitations of the current analysis and prompt further research to explore these factors in more detail. This could involve conducting prospective studies with more comprehensive data collection to address potential confounding and provide more robust evidence.

Future research should focus on the following areas:

Prospective, longitudinal studies: Prospective studies are essential to establish causal relationships between identified risk factors and CHD. Longitudinal designs that follow individuals from preconception to birth and beyond can provide valuable insights into the timing and cumulative effects of exposures on CHD development. These studies can help elucidate the mechanisms underlying the observed associations and provide a stronger basis for targeted interventions.

Combined effects of multiple risk factors: Investigating the combined effects of multiple risk factors is crucial for understanding the complexity of CHD etiology. Future research should explore how various risk factors interact and synergistically contribute to the risk of CHD. This can help develop comprehensive risk assessment models that consider the cumulative impact of multiple factors and guide preventive interventions effectively.

Genetic basis of CHD: Further exploration of the genetic basis of CHD is warranted. Advances in genomic technologies and large-scale genetic studies can help identify specific genetic variants and pathways associated with CHD. Understanding the genetic underpinnings of CHD can shed light on the underlying mechanisms, aid in risk stratification, and potentially lead to targeted interventions or therapies.

Evaluation of folic acid supplementation regimens: Although folic acid supplementation has shown benefits in reducing the risk of CHD, further research is needed to optimize its preventive potential. Investigating the impact of different folic acid supplementation regimens, such as varying dosages or timing of supplementation, can provide insights into the most effective strategies for CHD prevention. This research can inform guidelines and recommendations for folic acid supplementation in pregnant women.

AUTHOR CONTRIBUTIONS

Yaowu Zhan and Jinxiu Bai contributed equally.

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