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Relationship between Vitamin D Consumption during Pregnancy and Neonatal Congenital Heart Disease

Mohammad Hosein Arjmandnia[1], Mostafa Vahedian[1], Maryam Yousefi[1], Mehrnam Amouei[2], Sajjad Rezvan[2], Mohammad Hossein Assi[1], Millad Siamaki, Akram Barati[1], Amir Hossein Naderi[1*], Ali Reza Sharifi[1]

[1] *Qom University of Medical Sciences, Qom, Iran*
[2] *Rafsanjan University of Medical Sciences, Rafsanjan, Iran*

* ***Corresponding author:*** Amir Hossein Naderi, Qom University of Medical Sciences, Qom, Iran. Tel: +989191721728; Email: naderi.amirh@gmail.com

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Background and Aim: Interactions between genetic and environmental factors, including modifiable maternal nutrition and lifestyle, play a significant role in the pathogenesis of most congenital heart defects (CHD). This study was conducted to investigate the relationship between periconceptional maternal vitamin D status and the prevalence of CHD in offspring.

Materials and Methods: This case-control study was conducted on 660 neonates referring to Masoumeh Hospital, Qom, Iran, from April 2016 onwards. The subjects were divided into two groups of CHD and healthy patients. The instrument applied to collect the necessary data was a research-made checklist including demographic data and risk factors related to the study, which was filled by mothers. Independent t-test and Chi-square test were used to analyze quantitative and qualitative variables, respectively. A logistic regression test was also utilized, and the p-value of less than 0.05was considered significant.

Results: The mean age of mothers was obtained as 30 years in both groups. It was revealed that 94 (28.5%) and 159 (48.2%) of mothers in the case and control groups consumed Vitamin D in pregnancy. There was a significant difference between vitamin D intake and CHD in the two groups(p<0/001). The economic status of 53.3% of families with CHD patients was reported to be low. According to the results, 70.6% of mothers in the case group were highly educated.

Conclusion: Based on the results, vitamin D consumption during pregnancy was associated with the reduction of neonatal CHD. Moreover, economic status was found as another risk factor affecting the development of neonatal CHD.

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Introduction

The neonates with heart defects can cause major problems; for example, children with congenital heart disease (CHD) are at risk for stunted growth (1-3). Moreover, CHDs are major causes of infant and child mortality(4). On the other hand it should be noted that CHD is one of the most common birth defects (5, 6), highlighting the necessity of performing more research in this domain. The literature review indicated that the prevalence of CHD showed an increasing trend by more than 50% from 2000-2010 (7). About two-thirds of such patients are diagnosed at an older age; however, this late diagnosis can increase complications.

Although extensive research has been conducted on known risk factors for the prevalence of CHD, this issue is still of interest to many researchers and students (8). For instance, the prevalence of CHD has been shown to increase sharply with maternal obesity. Nonetheless, this research is not merely devoted to proven risk factors. Another study showed beneficial effects of maternal residential greenness on CHDs (9). The prevalence of CHD is not limited to environmental factors. Regarding this, the findings of a study were indicative of an

increased level of high-density lipoprotein 3 cholesterol with a reduced incidence of heart disease (11-13).

The other issue that has been addressed in studies is psychological problems. The results of a study suggested that maternal stress during heart formation may be a risk factor for the development of CHD in neonates (14). In addition, maternal age, even without causing chromosomal problems in the fetus, such as Down Syndrome, can be considered a risk factor for CHD as aging increases the chances of developing this disease (15-21). One of the other factors being studied includes alcohol consumption during pregnancy. According to the results of a study, even low alcohol consumption can have a negative effect on heart development and lead to heart cell defects and CHD incidence (22, 23). Maternal smoking during pregnancy is also a known risk factor for the development of CHD (26-24). In this regard, although a large percentage of CHD have an unknown origin (27), smoking during pregnancy alone accounts for 1.4% of CHD cases. The findings of recent studies have shown that smoking dose can also play a role in the development of this disease.

The effect of consuming multivitamins and folic acid in early pregnancy and even before pregnancy was demonstrated in preventing CHD incidence in recent studies. In this respect, in another study, the researchers were suggested to take this finding into consideration for performing further studies (27, 28). In another recent study, it was found that vitamin D intake was directly related to a reduction in the incidence of cardiovascular disease among neonates (29). Considering these results, it can be concluded that CHD is an issue that cannot be simply ignored, since not only does it pose problems to families but also it will impose huge costs on society. Furthermore, given that women in Iranian society often struggle with vitamin D deficiency, it seems necessary to study the effects of this issue in various conditions on females, especially during pregnancy. Consequently, this study was conducted to examine the consumption of vitamin D and its relationship with congenital cardiovascular disease, as well as several other factors as sub-objectives.

Materials and Methods

Study sample

This case-control study was performed on patients, born from March 2016 onwards, referring to the heart clinic of Hazrat Masoumeh Hospital, Qom, Iran. The subjects with congenital cardiovascular disease those with healthy hearts were categorized as the case and control groups. The population of this study (n=660) was studied in two groups (n=330 each) of CHD positive (case group) and CHD negative (control group). The mean scores of maternal age in the case and control groups were obtained as 30±7.12 and approximately 30±7.25 years, respectively.

Study phases

To control the confounding variables, the groups were matched in terms of the homogeneity of a number of identified risk factors, such as a history of gestational diabetes and maternal smoking and alcohol consumption. The only inclusion criterion was having any congenital cardiovascular disease. The instrument used to collect the necessary data was a researcher-made checklist that assessed the variables of CHD and vitamin D with calcium consumption. Moreover, confounding factors, such as maternal age at delivery, infant gender, parental financial status, parental education level, history of CHD in first-degree relatives (i.e., father, mother, sister, and brother) was also examined using the checklist. The necessary data were collected, followed by the evaluation of qualitative variables, using frequency and percentage, and quantitative variables, using mean and standard deviation.

Statistical analyzes

The sample size was calculated using the volume formula of the logistic regression model for the qualitative response variable and considering the probability of type I error of 5%, power of 0.8, and odds ratio of 0.76 based on the study performed by Botto et al. (28). Accordingly, the minimum sample size was estimated at 660 cases, which were divided into two groups of 330 patients and 330 healthy subjects. An independent sample t-test was used to analyze the quantitative variables of the studied groups. In this study, a p-value of less than 0.05 was considered significant.

Results

Regarding the use of vitamin D during pregnancy, it was revealed that 94 (28.5%) and 159 (48.2%) cases had vitamin D in the case and control groups, respectively.

Initially, the case and control groups were compared in terms of vitamin D intake and its relationship with CHD . In general, 94 and 159 mothers in the case and control groups had vitamin D intake, respectively, indicating a relatively significant difference between the two groups in this regard (Table 1).

In this study, 49.4% and 50.6% of the subjects in the case group and 50.6% and 49.4% of the cases in the control group were males and females,

Table 1. Contingency table of the relationship between previous abnormalities and vitamin D intake

Congenital heart disease		Vitamin D uptake		Total	P-value
		Yes	No		
Positive	Number	94	236	330	0.000
	Percentage	28.5%	71.5%	100.0%	
Negetive	Number	159	171	330	
	Percentage	48.2%	51.8%	100.0%	
Total	Number	253	407	660	
	Percentage	38.3%	61.7%	100.0%	

respectively. Considering the economic status of the families, 53.3% and 43.6% of the patients in the case and control groups suffered from poor economic status, respectively. According to the results, 29.4% and 37.3% of the parents in the case and control groups had under diploma degree, respectively, and the rest of the parents in both groups held higher degrees.

The results of the Chi-square test (x^2=4.61, P-value=0.03) showed that 22.7% of the relatives in the case group had a history of heart abnormalities, while in the healthy group 11.8% of The relatives of the healthy group had a history of heart abnormalities and 88.2% of the rest had no history of heart abnormalities (Table 2).

The mean age scores of mothers in the case and control groups were estimated at approximately 30±7.12 and 30±7.25 years, respectively (Table 3).

Table 2. Relationship between variables in both case and control groups

Congenital heart disease		Neonatal gender		Total	P-value
		Male	Female		
Positive	Number	163	167	330	0.76
	Percentage	49.4%	50.6%	100.0%	
Negative	Number	167	163	330	
	Percentage	50.6%	49.4%	100.0%	
Total	Number	330	330	660	
	Percentage	50.0%	50.0%	100.0%	
Congenital heart disease		Economic status		Total	0.01
		Good	Low		
Positive	Number	154	176	330	
	Percentage	46.7%	53.3%	100.0%	
Negative	Number	186	144	330	
	Percentage	56.4%	43.6%	100.0%	
Total	Number	340	320	660	
	Percentage	51.5%	48.5%	100.0%	
Congenital heart disease		Parental education		Total	P-value
		Under diploma	Higher than diploma		
Positive	Number	97	233	330	0.03
	Percentage	29.4%	70.6%	100.0%	
Negative	Number	123	207	330	
	Percentage	37.3%	62.7%	100.0%	
Total	Number	220	440	660	
	Percentage	33.3%	66.7%	100.0%	
Congenital heart disease		History of congenital heart disease in family		Total	P-value
		Yes	No		
Positive	Number	75	255	330	0.000
	Percentage	22.7%	77.3%	100.0%	
Negative	Number	39	291	330	
	Percentage	11.8%	88.2%	100.0%	
Total	Number	114	546	660	
	Percentage	17.3%	82.7%	100.0%	

Table 3. Independent t-test results of maternal age in the two groups

	Congenital heart disease	n	Mean	SD	P-value
Maternal age	Yes	330	29.96	7.12	0.75
	No	330	30.13	7.25	

Discussion

The interaction between genetics and environmental factors, including changing variables in maternal nutrition and lifestyle, plays an important role in the pathogenesis of CHD. Given the fact that females in Iranian society often struggle with vitamin D deficiency, the effects of this deficiency in various conditions on women in society, particularly during pregnancy, were investigated in this study. The results of the present study showed a significant relationship between maternal vitamin D intake and heart defects in neonates. Regarding this, vitamin D intake could reduce the risk of heart abnormality development. No significant relationship was observed between neonatal gender and heart abnormalities.

It was revealed that neonates born in families with higher education than diploma were more likely to develop heart defects. Moreover, the likelihood of developing heart abnormality was higher among newborns with a positive family history of heart disease. In the current study, there was no significant difference between the two groups in terms of maternal age. Several studies examined the relationship between maternal vitamin and other micronutrient intake and neonatal CHD development (26, 32, 33).

The present study merely investigated the effect of vitamin D consumption. In research conducted by Koster et al. (2018), the amount of maternal vitamin D consumption was estimated using gathered data from the maternal body mass index, multivitamin supplementation, and race, as well as the season that mothers' blood samples were collected. Subsequently, vitamin D level in the mother's body was classified into three categories, namely adequate, moderate, and inadequate. According to the results of this study, insufficient or moderate levels of vitamin D in the mother's body were associated with an increased risk of CHD (29). In our study, the levels of maternal vitamin D intake were not measured; rather, the consumption or non-consumption of vitamin D was checked by a checklist. Accordingly, it was revealed that vitamin D intake decreased the incidence of CHD in neonates, which was in agreement with the results of the research conducted by Koster et al. (2018).

Due to the low prevalence of CHD manifestation during infancy, default studies at the birth time are not sufficient to determine the true risk of CHD development. Consequently, this case-control study was carried out with the standardized time determined as after neonatal birth. Dilli et al. reported that serum vitamin D levels in both mothers and neonates were relatively low, indicating that these ratios were effective in the pathogenesis of CHD (30).

The increased level of some nutrients can have a teratogenic effect, whereas vitamin D is beneficial for the development of the fetal heart. Vitamin is involved in the process of binding the active form of vitamin D to its receptor. This receptor is involved in gene regulation (31). Vitamin D receptor is present in all cells and affects many processes if activated. Embryogenesis and cardiogenesis occur between 2 and 7 weeks of gestation which require the regulation of a group of genes (32). The results of recent studies have shown that components of the vitamin D pathway are involved in cardiogenesis (33). The reduction level of 25-hydroxyvitamin D will lead to a reduction in its active type, which consequently affects gene regulation. This finding is supported by evidence demonstrating that the probability of CHD and other diseases development increases with the reduction in vitamin D levels (34).

Conclusion

Our study showed that the non-consumption of vitamin D can cause an increase in neonatal CHD incidence. However, further studies are required to be performed in this domain since the adequate and safe intake of nutritional and industrial vitamin D for this group has not been determined yet.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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