Health and Development Journal

Winter 2021, Volume 10, Number 1

Health and Development Journal 2021; 10(1):1-9
http:// jhad.kmu.ac.ir//

Research Paper

Health and Development Journal

Open Access Publish Free

Factors Related to Genetic Disorders and Congenital Anomalies in Nogab Village of South Khorasan Province

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Citation: Masinaei Nejad ME, Khanjani N, Khodadadi M, Najafi E. Factors related to genetic disorders and congenital anomalies in Nogab village of south Khorasan province. Health and Development Journal. 2021; 10(1):1-9.
10.22062/jhad.2021.91580

Received: 23.02.2020
Accepted: 21.09.2020

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Abstract

Background: Congenital malformations are defects that are present at birth. The purpose of the present study was to determine the status of congenital malformations and their risk factors in Noghab village, South Khorasan Province.

Methods: In this case-control study, 152 cases with congenital anomalies and 152 controls were enrolled. A researcher-made checklist and face-to-face interviews were used to record patient data. Chi-square test, Mann-Whitney U, and univariate and multivariate logistic regression in SPSS 22 were used for statistical analysis.

Results: One hundred and nineteen (72.5%) patients were male. The overall prevalence of congenital abnormalities in the village was 4.5%. The most prevalent types of disorders were neurological (35.4%) and multiple abnormalities (30.5%). According to multivariate logistic regression, consuming barberries daily during pregnancy, having first-degree relatives with anomalies, daily use of herbal medicine and weekly consumption of pickled vegetables during pregnancy, and the existence of a chronic disease in the father were significantly associated with congenital disorders in the offspring.

Conclusion: In addition to the previously known risk factors for congenital malformation, consumption of barberries, herbal medicine and pickled vegetables during pregnancy, might be risk factors for congenital anomalies. These products should be used with caution in pregnant women.

Keywords: Genetic disorders, Congenital anomalies, Barberry, Prevalence, Iran

Introduction

Congenital anomaly refers to a permanent change that is caused before birth by an evolutionary disorder of internal origin, in the body structure. According to the World Health Organization (WHO), congenital abnormalities include single or multiple structural, functional, or biochemical-molecular defects that are present at birth and are detectable (1). Congenital malformations are among the most important causes of hospitalization, disability and infant death (2). The WHO has reported the prevalence of congenital anomalies as 1.27 percent, while its prevalence in Iran varies from 2.01 percent in Ahvaz, to 3.5 percent in Tehran (3, 4). The pattern of congenital anomalies at different times and at different geographical points may be different and represents the complex interaction of known and unknown genetic and environmental factors, including social, racial, and cultural variables (5, 6).

Currently, congenital birth defects are the most important cause of infant mortality, especially in developed societies, and the third leading cause of death and disability in children in developing countries. Therefore, countries should allocate resources to prevent or control the incidence of these anomalies in the future (7, 8). Although national development, and the improvement of healthcare and immunization has significantly reduced the prevalence of infectious diseases and nutritional disorders in the Eastern Mediterranean region in recent years, but genetic disorders and congenital anomalies still pay a significant contribution to prenatal and neonatal mortality in many countries in this region (9, 10). Although most congenital abnormalities have genetic causes, more than 20% of them are caused by environmental and teratogenic factors during the fetal period (11). These factors can cause a significant part of these anomalies through genetic mutations (12).

Many of the factors that cause congenital anomalies are preventable and can vary depending on the geographical and cultural differences of communities. Davari et al. found an association between congenital anomalies and consanguineous marriage, history of drug use, history of anomalies in the family, and mothers' age (above 35 or below 18) in Isfahan, Iran (11). However, in the study conducted about the incidence of obvious congenital anomalies in live neonates born in the Mobini Hospital in Sabzevar, in 2005-2006, no significant relation was observed between the type of anomaly and parents' familial relationship (13); or in the study of Masoodpoor et al. about the frequency and pattern of congenital anomalies in live neonates born in Niknafs Hospital, Rafsanjan, Iran, in 2007-2008, no statistically significant relation was reported between apparent congenital anomalies and the mothers' underlying disease, consanguineous marriage of the parents or maternal age (4).

Noghab village is located 18 km west of Darmian city and 90 km east of the capital city of South Khorasan province (Birjand). The population of this village in 2016 was 3650 people and 900 households, with an average household size of 4.05 persons. The high number of congenital anomalies and genetic disorders are prominent features of this village.

The annual production of barberry in this village is about 600 tons, and it is the first rank producer of this product in South Khorasan province, when compared according to area size. Some researchers believe that it is better to avoid barberry consumption during pregnancy (14) and barberry consumption during this period may cause increased uterine contractions (15). Shariatzadeh et al. studied the teratogenic effects of blue barberry extract on the liver tissue of Syrian mice embryos and concluded that administering barberry extract to pregnant mice can cause abnormal development of the fetus (16).

However, as far as we know, no study has been done about the teratogenic effects of barberries in humans, and the causes of congenital anomalies is probably different at different times and places. Due to the high incidence of congenital anomalies in this village, the present study investigated the possible causes of these anomalies.

Methods

The present study was a case-control study in which 152 patients with congenital anomalies and the same number of healthy individuals were selected from the population of Noghab village, in 2016, by individual matching based on gender and age ± 1 month.

The cases were laboratory confirmed congenital anomaly cases. For those who did not undergo the laboratory tests, the diagnosis was made by a physician and based on the individual's clinical and physical symptoms and available documents.

Controls were selected from individuals that were claimed to be healthy by the physician, and were individually matched. Sampling of patients was done from the available population of this village and sampling of healthy individuals was done from the vital statistics of the health house separately. Individuals over the age of 50, those who had died or whose mother had died or refused to cooperate were excluded from the study. Individuals whose mothers were not alive at the time of data collection, were excluded from the study, because it was not possible to ask questions about their exposure during pregnancy.

The proposal of this research was reviewed and approved by the standing ethics committee of Kerman University of Medical Sciences (IR.KMU.REC.1395.386). After obtaining the consent of the participants and/or their parents, and informing them about the objectives of the research and the confidentiality of the information, and their right to withdraw from the research, their informed consent was obtained. Then the researcher-made checklist was completed, based on recorded information and face-to-face or telephone interviews with the mothers. The information received was matched with the information of the patient's health record and the information collected by the health worker, working in the village, and if there was a discrepancy, the information recorded in the documents was preferred.

General information about the village, including the number of couples living in the village, number of consanguineous marriages (by determining the degree of kinship), number of marriages within the village, and number of families with disabled children, was extracted from the medical records of the health center, and the information collected by the health worker, working in that unit. The checklist consisted of 47 questions, which included questions about personal information of the patient and her/his parents, information about family history, previous pregnancies, the situation during the pregnancy of the child with anomaly, and questions about the production and consumption of barberry.

The face and content validity of the checklist was verified with the help of several academics. Finally, the data were entered into SPSS-22 software and analyzed using Chi-square, Mann-Whitney U, and univariate and multivariate logistic regression, with a significance level of $p < 0.05$.

Results

The number of congenital disorders and anomalies in 2016 was 164 in the total population of Noghab village. Out of 164 patients in the village, 3 were over 50 years old, and 7 patients had lost their mother and were excluded. Two patients and their families did not accept to enter the study. Therefore 152 patients were enrolled in this study.

The overall prevalence of congenital disorders and anomalies was 4.51% in the total population of this village. 16.7% of households (147 households) had at least one disabled child. The most common disorders were neurological disorders, which were seen in 35.4 % (58 out of 164), and 30.5 % (50 out of 164) had multiple anomalies. Table 1 shows the frequency of congenital disorders and abnormalities, in terms of demographic variables in patients enrolled in this study.

The mean age of mothers at the time of the patients' birth was 28.0 ± 6.2 in the case group, and 26.5 ± 6.3 in the control group, and was significantly different ($p = 0.02$), and the mean age of fathers in the case group was 33.9 ±10.3, and in the control group was 30.5 ± 7.6 years, and was significantly different ($p = 0.002$) as well. But mothers age (as a categorical variable, in age range groups) was not significantly different between the case and control groups ($p = 0.22$).

There was no significant difference between parents' education ($p=0.10$ for mother's education and $p=0.15$ for father's education), type of delivery ($p=0.64$) and duration of pregnancy ($p=0.26$) in case and control groups. In the village, the overall prevalence of first-degree consanguineous marriages was 25.1% (221 couples), second-degree consanguineous marriages was 11% (97 couples) and distant or unrelated consanguineous marriages were 63.9% (562 couples). Although there was a significant relation between the couple's familial relationship and the incidence of congenital disorders in the univariate model, this variable was not significant in the multivariate model. Among the 50 patients with a history of congenital anomalies in their second-degree relatives, in the case group (Table 2), 72% (36 patients) had a maternal relationship with this relative, but in the control group, only 36.4% had a maternal relationship.

The prevalence of inter-village marriages (both husband and wife originally from the village) among these rural couples was 91.1% of all households (802 households), in which 15.2% of these marriages (122 couples out of 802 couples) had led to a disabled child.

Table 1. Frequency of congenital disorders and abnormalities in terms of demographic variables in rural patients

Variable	Variable levels	Frequency (%)	Prevalence (number in 100 people) 95% range	Chi-square p-value
Gender	Male	109(71.71)	5.88 5.84-5.92	≤0.001
	Female	43(28.29)	2.41 2.39-2.43	
Age group (years)	Under 15	34(22.37)	2.77 2.74-2.79	0.015
	15 to <25	57(37.50)	8.64 8.59-8.68	
	25 and over	61(40.13)	3.49 3.46-3.52	
Father's level of education	Illiterate	45(29.61)	35.71 35.63-35.79	≤0.001*
	Elementary	90(59.21)	21.42 21.35-21.49	
	Middle School	12(7.89)	4.41 4.38-4.44	
	Diploma	4(2.63)	12.9 12.84-12.95	
	Academic	1(0.66)	3.33 3.30-3.36	
Mother's level of education	Illiterate	51(33.55)	32.28 32.20-32.35	≤0.001*
	Elementary	99 (65.13)	20.54 20.48-20.60	
	Middle School	1(0.66)	0.50 0.49-0.51	
	Diploma	1(0.66)	2.78 2.75-2.80	
	Academic	0(0.00)	0.00 0.00-0.00	
Familial marriage	First degree relative	55(36.18)	23.91 23.84-23.98	0.59
	Second degree relative	45(29.61)	44.55 44.47-44.63	
	Far relative / Not related	52(34.21)	8.89 8.84-8.93	
Type of disorder	Neurological	55(36.18)	1.72 1.70-1.74	≤0.001*
	Multiple anomaly	45(29.61)	1.40 1.38-1.42	
	Musculoskeletal	31(20.39)	0.97 0.95-0.99	
	Chromosomal	17(11.18)	0.53 0.52-0.54	
	Digestive	2(1.32)	0.06 0.056-0.064	
	Urogenital	1(0.66)	0.03 0.027-0.033	
	Cardiovascular	1(0.66)	0.03 0.027-0.033	
Patient's birth season	Spring	49(32.24)	6.57 6.53-6.60	0.019
	Summer	46(30.26)	5.21 5.17-5.24	
	Fall	31(20.39)	4.28 4.25-4.31	
	Winter	26(17.11)	3.07 3.04-3.10	
	Total	152(100)	4.75 4.72-4.78	-

* Fisher's exact test

Table 2. Comparison of qualitative variables in case and control groups based on univariate logistic regression

Variable		Group Control N (%)	Case N (%)	Chi-square p-value	Crude OR	95% CI
Mother's level of education	Literate	114(75.00)	101(66.45)	0.101	1	1
	Illiterate	38(25.00)	51(33.55)		1.51	0.92-2.49
Father's level of education	Literate	118(77.63)	107(70.39)	0.15	1	1
	Illiterate	34(22.37)	45(29.61)		1.46	0.87-2.45
Weight of baby at birth	< 2500 grams	127(98.45)	107(91.45)	0.011	1	1
	≥ 2500 grams	2(1.55)	10(8.55)		5.93	1.27-27.68
Familial marriage	Far relative / Not Related	82(53.95)	52(34.21)	0.002	1	1
	First degree relative	34(22.37)	55(36.18)		2.55	1.47-4.43
	Second degree relative	36(23.68)	45(29.61)		1.97	1.13-3.45
Parity	2nd to 4th pregnancy	74(48.68)	75(49.34)	0.019	1	1
	First pregnancy	46(30.26)	28(18.42)		0.60	0.34-1.06
	5th or more	32(21.06)	49(32.24)		1.51	0.87-2.62
Folic acid consumption in the mother during pregnancy	Consumed regularly	33(21.71)	24(15.79)	≤0.001	1	1
	Consumed sometimes	61(40.13)	34(22.37)		0.77	0.39-1.5
	Did not consume	53(34.87)	88(57.89)		2.28	1.22-4.27
	Does not know	5(3.29)	6(3.95)		1.65	0.45-6.04
Iron consumption in the mother during pregnancy	Consumed regularly	35(23.02)	36(23.68)	0.063*	1	1
	Consumed sometimes	68(44.74)	49(32.24)		0.70	0.39-1.27
	Did not consume	44(28.95)	64(42.11)		1.41	0.77-2.58
	Does not know	5(3.29)	3(1.97)		0.58	0.13-2.63
Multi-vitamin consumption in the mother during pregnancy	Consumed regularly	37(24.34)	32(21.05)	0.013*	1	1
	Consumed sometimes	66(43.42)	48(31.58)		0.84	0.46-1.53
	Did not consume	44(28.95)	69(45.40)		1.81	0.99-3.32
	Does not know	5(3.29)	3(1.97)		0.69	0.15-3.13
Mother's underlying illness	No	121(79.61)	105(69.08)	0.036	1	1
	Yes	31(20.39)	47(30.92)		1.75	1.03-2.95
Daily intake of saffron during pregnancy	Less than 3 strands	149(98.03)	136(89.47)	0.002	1	1
	3 strands and more	3(1.97)	16(10.53)		5.84	1.67-20.49
Daily Tobacco use during pregnancy	No	151(99.34)	144(94.74)	0.036*	1	1
	Yes	1(0.66)	8(5.26)		8.39	1.04-67.9
Father's classified age	18-35 years	114(75.00)	92(60.53)	0.007	1	1
	Over 35 years	38(25.00)	60(39.47)		1.96	1.2-3.19
A second-degree relative with an anomaly	No	128(84.21)	102(67.10)	0.001	1	1
	Yes	24(15.79)	50(32.90)		2.61	1.51-4.54
Pre-pregnancy counseling	Yes	8(5.26)	12(7.89)	0.35	1	1
	No	144(94.74)	140(92.11)		1.54	0.61-3.89
At least 6 times prenatal care visits during pregnancy	Yes	41(26.97)	36(23.68)	0.51	1	1
	No	111(73.03)	116(76.32)		1.19	0.71-1.99
Daily consumption of barberry during pregnancy	Less than a tablespoon	146(96.05)	70(46.05)	≤0.001	1	1
	A tablespoon and more	6(3.95)	82(53.95)		28.50	11.86-68.48
A first-degree relative with anomalies	No	148(97.37)	91(59.87)	≤0.001	1	1
	Yes	4(2.63)	61(40.13)		24.80	8.72-70.50
Daily use of herbal medicine during pregnancy	No	147(96.71)	101(66.45)	≤0.001	1	1
	Yes	5(3.29)	51(33.55)		14.85	5.72-38.50
Weekly consumption of pickles during pregnancy	3 times or less	151(99.34)	147(96.71)	0.099*	1	1
	More than 3 times	1(0.66)	5(3.29)		5.14	0.60-44.50
Father's underlying illness	No	140(92.11)	121(79.61)	0.002	1	1
	Yes	12(7.89)	31(20.39)		2.99	1.47-6.08

* Fisher's Exact test.

Meanwhile, a higher number, which was 30 out of 78 (38.4%) of couples which only one of them was originally from this village had children with disabilities.

The average annual barberry production of 78 households (25.7%) was over 100 kg. The annual barberry production variable was not normal, and the Mann-Whitney U test, showed that there was a significant difference between barberry production in the case and control groups ($p < 0.001$).

In this group of mothers, *Curcuma zedoaria* with 35.2% (18 people), Anise with 33.3% (17 people) and Dillweed with 27.4% (14 people) had the highest consumption. But in the control group, only 5 mothers took herbal medicines and none of the mothers reported taking the above three herbal medicines. Therefore, there was a significant relation between the use of herbal medicine and anomalies (Table 2).

In multivariate logistic regression, only some variables were significant, that have been shown in Table 3. These variables included daily consumption of barberry during pregnancy, first-degree relatives with anomalies, daily consumption of herbal medicine, weekly consumption of pickles during pregnancy, and the father suffering from a chronic disease. The Hosmer and Lemeshow statistic in this model was 0.82.

Table 3. Comparison of qualitative variables in case and control groups based on multivariate logistic regression

Variable		Group		P-value	Adjusted OR	95% CI
		Control N (%)	Case N (%)			
Daily consumption of barberries during pregnancy	Less than a tablespoon	146(96.05)	70(46.05)	≤ 0.001	1	1
	A tablespoon and more	6(3.95)	82(53.95)		39.69	14.92-105.57
A first-degree relatives with anomalies	No	148(97.37)	91(59.87)	≤ 0.001	1	1
	Yes	4(2.63)	61(40.13)		33.15	10.44-105.24
Daily use of herbal medicine during pregnancy	No	147(96.71)	101(66.45)	≤ 0.001	1	1
	Yes	5(3.29)	51(33.55)		18.07	6.03-54.15
Weekly consumption of pickles during pregnancy	3 times or less	151(99.34)	147(96.71)	0.099*	1	1
	more than 3 times	1(0.66)	5(3.29)		15.71	1.44-171.55
Father's underlying illness	No	140(92.10)	121(79.60)	0.002	1	1
	Yes	12(7.90)	31(20.40)		2.99	1.47-6.08

* Fisher exact test.

Discussion

This study showed that in 2016, the overall prevalence of congenital anomalies in Noghab village was 4.5%, which is higher than the pooled average reported by Daliri et al. for Iran, which was 1.8%, and the prevalences reported by Dastgiri et al. in northwestern Iran (1.65%), Tootoonchi et al. in Tehran (2.3%), Karbasi et al. in Yazd (2.8%), and Akbarzadeh et al. in Sabzevar (3.1%) (13, 17-20).

Part of this high incidence may be related to the fact that there is no obstetrics or ultrasound facility in Noghab village, and therefore mothers cannot use routine professional health and medical care, before and during childbirth (21).

According to reports, the global prevalence of congenital anomalies is 3 per 1000 live births. However, the prevalence of congenital anomalies in Iran is much higher than the global average and this number was 18 per 1000 live births during the years 2000-2016 (17). In the present study, the prevalence of genetic disorders and congenital anomalies was even higher than the national average.

In this study, neurological disorders had the highest prevalence of abnormalities, and cardiovascular disorders had the lowest prevalence. These results are inconsistent with the results of Masoodpoor et al. in Gorgan, Akbarzadeh et al. in Sabzevar and Khatami et al. in Mashhad, Iran, in which musculoskeletal and urogenital anomalies were more common (2, 4, 13). But is consistent with the study conducted by Singh et al. in Nigeria (22). The frequency and different patterns of congenital anomalies in different regions may be due to different racial, ecological, social, economic and environmental risk factors, study methods and differences in the classification of anomalies.

In the present study, the highest number of patients were born in spring and summer, respectively, which is not consistent with the study of Akbarzadeh et al. in Sabzevar, in which the highest number of anomalies were born in autumn and winter (13). In Nooghab village, during the last 5 years, most abortions occurred in the second half of each Persian year, which is in fall and winter. These babies would have been born in the first half of next year (spring and summer), if abortion had not happened.

Barberry is one of the most important sources of income in this village and barberry is harvested from early October to mid-November every year. In the present study, barberry consumption during pregnancy was identified as a strong risk factor for disorders, and the annual barberry production variable was significantly related with anomalies, as well. These findings are consistent with a study conducted by Messinaei in Darmian city that also found the consumption of barberries during pregnancy may be a risk factor for congenital anomalies (23), a study by Shariatzadeh et al. in Iran which stated that administering 40 mg/kg of barberry extract during pregnancy, in mice, causes fetal anomalies (16), and a study conducted by Chuang et al. in Taiwan who reported that Berberine (a chemical found in barberries) consumption in the first trimester of pregnancy increases the chance of developing neural congenital anomalies, more than eight times (24). Perhaps one of the reasons for the high prevalence of neurological disorders and the different type of congenital disorders in the present study in comparison with other studies, is the high consumption and production of barberries in this village. Barberries contain alkaloid compounds, especially berberine, phenolic and triterpenoid (24, 25).

In the present study, the history of chronic diseases in the father was considered as a risk factor for genetic disorders. However, in some studies, the mother's underlying disease was reported as a risk factor (26). Also, in this study, the existence of relatives with congenital anomalies or genetic disorders were identified as risk factors for congenital anomalies, which is similar to the findings of Davari et al. in Isfahan and Bishop et al. in Kenya (11, 27). In this study, most (72%) of the patients who had a second degree family member with a congenital disorder, were related with this family member from the maternal side, and this is consistent with the results of Rabieyan et al. in Rasht (28).

In this study, the type of delivery had no effect on the occurrence of abnormalities, which is consistent with Khatami et al.'s study conducted in Mashhad (2).

Based on multivariate logistic regression there was no significant relation between parents familial relationship and the incidence of congenital anomalies, in this current study, and this is consistent with the studies conducted by Akbarzadeh et al. in Sabzevar, Bromiker et al. in Palestine and Jalali et al. in Kermanshah (13, 26, 29). But, is in contrary with the studies conducted by Davari et al. in Isfahan, Akbarzadeh et al. in Sabzevar, Akrami in Iran, Ghorbani et al. in Golestan province of Iran, and Bishop et al. in Kenya (11, 13, 27, 30, 31). The prevalences of consanguineous marriages in Iran vary between 30 to 85% (32), but in our study this prevalence was 36.1%. Therefore, the lack of relation between this variable and congenital anomalies in this study, is not far from expectation.

The findings of the present study showed that the prevalence of congenital anomalies was higher in males, and this is in line with the results of Daliri et al. in Iran, Faal et al. in Birjand, Davari et al. in Isfahan and Akbarzadeh et al. in Sabzevar (11, 13, 17, 33).

In this study, low birth weight was not associated with congenital anomalies, which is not consistent with the results of Tootoonchi et al. in Tehran and Black et al. in the United States (20, 34). Also, the pregnancy rank variable was not a risk factor in the occurrence of congenital anomalies in this current study and this is consistent with the studies of Khatami et al. in Mashhad and Alijahan et al. in Ardabil (2, 35). The household dimension was not a risk factor in our study either.

Although herbal products are often used throughout pregnancy around the world, studies show that consuming these products may be dangerous for the fetus. There is currently insufficient evidence on the safety of plant products during pregnancy and its effect on genetic disorders and congenital anomalies (36, 37). In the present study, more than one third of the mothers in the case group used at least one herbal medicine and more than half of them mentioned the consumption of barberries more than 5 grams per day in their pregnancy, therefore, the use of herbal medicine may be a risk factor for congenital anomalies. In the Moussally study, different types of herbal medicine including flax, green tea, chamomile and black pea were studied, and none of them were risk factors for genetic or congenital anomalies (36). But in the present study, *Curcuma zedoaria*, *Tanacetum parthenium*, anise (*Foeniculum vulgare*), dillweed, sage (*Teucrium polium*) and *Hyssopus officinalis* were used, which definitely have different effects.

In a study conducted in Kerman, 71% of mothers reported a history of taking at least one drug during pregnancy (38); and in this study, 33.5% of mothers in the case group reported using herbal medicine.

In the present study, consuming pickled vegetables during pregnancy was identified as a risk factor for congenital disorders, which may be due to increased sodium in the mother's body and its negative effect on fetal development (39). But no study was found about this relation, and more studies are needed.

In this study, according to multivariate logistic regression, taking folic acid and multivitamin supplements was not significantly associated with congenital disorders; and this is contrary to the results of a review done by Dehghani et al. in Iran, which stated that the use of multivitamins is a protective factor against congenital anomalies, and the study of Kirke et al. in Ireland which stated consumption of folic acid is a protective factor for these abnormalities (40, 41) as well. The reason for this result in the present study, is probably the stronger effect of other risk factors on the incidence of congenital anomalies. In this study, using iron supplementation was not significantly associated with the incidence of congenital disorders either, which was in line with the results of Alijahan et al. in Ardabil, and Messinaei in Darmian (23, 35).

In the present study, parents' age (as a quantitative variable) was a risk factor and older parents were more likely to give birth to a child with anomalies. This is consistent with the findings of Davari et al. in Isfahan, Khatami et al. in Mashhad and Dehghani et al. in Iran (2, 11, 40).

One of the limitations of this study was that it included only living people with congenital anomalies, and severe anomalies that had led to abortion, stillbirth and death were not included.

Children born with anomalies face a variety of educational, occupational, marital and social problems, and many die within the first five years of life. Therefore, by improving diagnosis and eliminating risk factors, the prevalence of these anomalies may decrease. Based on the available information, the prevalence of congenital anomalies is very high in Iran, and this causes significant invisible costs for individuals, communities and the health care system. Therefore, it is necessary to prevent congenital anomalies.

Conclusion

This study showed that in addition to the previously known risk factors for congenital malformation, consumption of barberries, herbal medicine and pickled vegetables during pregnancy, might be risk factors for congenital anomalies. These products should be used with caution in pregnant women.

Acknowledgments

This study was supported by grant number 95000099, from Kerman University of Medical Sciences. We also thank Birjand University of Medical Sciences for cooperating with us.

Conflict of interest

The authors have no conflict of interest.

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