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The relationship between the maternal consumption of barberry, saffron, pickled vegetables, and tea and the odds of congenital anomalies in Iranian children under 10 years of age: A case-control study

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Abstract:

BACKGROUND: The administration of barberry extract and saffron to pregnant mice has been reported to cause abnormalities in fetus development. Given the high cultivation of barberry and saffron in Qayenat, we aimed to investigate the association of the maternal use of barberry, saffron, pickled vegetables, and tea during gestation with Congenital Anomalies (CA) in Qayenat City, South Khorasan Province.

METHODS AND MATERIALS: The present case-control study was done on 150 patients under 10 years of age with CA (case group) and 150 healthy children that were selected for each case, with the same age (± 2 months) and sex, from the same town (control group) between March and May 2023. In this study, participants were included using convenient sampling in a consecutive manner. To control the possible confounding factors, and to identify independent risk factors for CA, multivariate logistic regression, adjusted odds ratios (ORs), and 95% confidence intervals (CIs) were carried out for this study.

RESULTS: More than 3 times pickled vegetable consumption in the week was also associated with an increased risk of CA (OR = 5.09; 95% CI: 1.66–15.55). More daily intake of barberry (more than a tablespoon) was associated with higher odds of CA (OR = 9.23; 95% CI: 3.42–24.90). There was no significant association between CA and daily intake of saffron ($P \geq 0.05$). Five and more than five cups of tea per day had a positive significant association with CA (OR = 3.21; 95% CI: 1.05–10.80).

CONCLUSIONS: In the present study, we found that maternal use of barberry, pickled vegetables, and tea during pregnancy were positively related to the odds of CA. Further detailed studies to determine the teratogenicity mechanism of these factors are recommended.

Keywords:

Berberis, congenital anomalies, Iran, pregnancy

Introduction

Congenital anomalies (CA) are described as functional or structural including metabolic disorders, present

at birth.^[1,2] CA is one of the main causes of hospitalization, neonatal mortality, and neonatal morbidity.^[3] According to the World Health Organization (WHO)

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statement, approximately 3% of infants and fetuses are born with major CA each year. Global studies have found that the incidence of CA births varies by geographical location and has been stated from 1.07% in Japan to 4.3% in Taiwan.^[4] The overall prevalence of CA among Iranian infants was estimated to be 2.3%.^[5]

Although several agents have been recognized as agents influencing CA such as genetic, environmental factors, and teratogens (including the mother's diabetes, exposure to chemicals or radioactive, drug use, infection, malnutrition, hyperthermia, and mother's addiction to alcohol), 66% of anomalies happen with unknown causes.^[5-7] It is estimated that about 94% of major birth defects occur in middle- and low-income countries.^[8] The difference in the pattern of occurrence of CA represents the complex interaction between known and unknown environmental and genetic factors, including social, cultural, racial, and ethnic factors.^[9,10] Since few studies have assessed the etiology of malformation in newborns, our knowledge about their causes is still limited.^[11]

Herbs are often thought to be natural and thus harmless. Pregnant women typically do not consult a physician or pharmacist for the use of herbal medicines. Many women have been shown to use many types of medicinal plants for different purposes during pregnancy such as reducing symptoms of pregnancy and helping fight infections.^[12] The safety of herbal medicines during pregnancy needs to be confirmed.^[13] Available findings are mostly inconsistent. A study conducted by Moussally *et al.*^[14] stated no relation between the consumption of certain herbal products (flax, peppermint, green tea, and chamomile) during pregnancy and the risk of low birth weight or CA. However, Kekana showed that the use of herbal medicine by black pregnant women in South Africa was associated with considerable unfavorable obstetric and perinatal outcomes.^[13] Shariatzadeh *et al.*^[15] observed that the feeding of 40 mg/kg extract of barberry fruit to pregnant mice may induce abnormalities in fetal growth and histological transformations of fetal liver tissue. Moreover, Masinaei Nejad *et al.*^[16] recently revealed that the use of barberries during pregnancy could be a risk factor for CA.

The current study was carried out in Qayenat city in southern Khorasan province. The area of the barberry gardens in this city is about 6500 ha, and annually about 7000 tons of dry barberry is harvested.^[17] South Khorasan, with an annual production of 15,000 tons of barberry, produces 98% of the country's barberry, and Qayenat is the largest producer in the world. In addition to barberry, a large amount of saffron is also cultivated in this city.^[18] According to some references, barberry and saffron should not be consumed during pregnancy and lactation,^[19,20] and the consumption of these products during this period leads to an increase

in uterine contractions and adverse effects on fetal growth especially in the last week of pregnancy.^[21,22] The administration of barberry extract to pregnant mice has been reported to cause abnormalities in fetus development.^[15] Given the high cultivation of barberry and saffron in Qayenat, we aimed to investigate the association of the maternal use of barberry, saffron, pickled vegetables, and tea during the gestation with CA in Qayenat City, South Khorasan Province.

Methods and Materials

Participants and study design

The present case-control study was done on 150 patients under 10 years of age with congenital disorders including musculoskeletal, urogenital, cerebrovascular, gastrointestinal, cardiovascular, and chromosomal disorders (case group) and 150 healthy children that were selected for each case, with the same age (± 2 months) and sex, from the same town (control group) between March and May 2023. In this study, participants were included using convenient sampling in a consecutive manner.

The inclusion criteria for the case and control groups included at least 10 years of residence of parents in Qayenat (before and after marriage). The participants in the case group had to have a confirmed diagnosis of CA recorded in their medical records or health files. In the control group, a physician confirmed that the child was healthy. In both groups, children whose mothers could not recall their food or medicinal consumption during pregnancy or who had died at the time this study was conducted, were excluded. All procedures performed in studies involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Khalkhal University of Medical Sciences (IR.KHALUMS.REC.1402.003). Informed consent was obtained from all the mothers and fingerprint was obtained from the Illiterate mothers which was approved by the Ethics Committee of the Khalkhal University of Medical Sciences.

Sample size

The sample size was calculated based on the following formula:

$$n = \frac{\{Z^{1-\alpha} / 2\sqrt{2p^2(1-p^2)} + Z_1 - \beta\sqrt{p^1(1-p^1) + p^2(1-p^2)}\}^2}{(p^1 - p^2)^2}$$

$$p^1 = \frac{(OR \times p^2)}{OR \times p^2 + (1 - p^2)}$$

($\alpha = 0.05$, $p^1 = 2 \times 0.2 \div 2 \times 0.2 + 0.8$, and $p^2 = 0.2$) and 150 subjects were calculated for each group.

Measures

Demographic and other required data were collected using a questionnaire which was made by the researchers. This questionnaire included the subjects' sociodemographic information such as gender, age, parents' age, parents' level of education, familial marriage, parents' underlying illness, number of times visited the health center for pregnancy care, birth weight, CA among first-grade relatives, abortion, still death, unwanted pregnancy, anemia in pregnancy, parity, intake of Iron, folic acid and multivitamin supplements in pregnancy, consumption of tea, pickles, barberry and saffron in pregnancy, number of children, daily tobacco use in pregnancy, substance abuse in pregnancy, and daily intake of drugs in pregnancy. How to gain weight during pregnancy (met, below, and exceed) was determined according to IOM pregnancy weight guidelines. Based on body mass index, people are divided into four groups (BMI: <18.5: underweight, BMI = 18.5–24.9: normal weight, BMI ≥25.0: overweight, and BMI ≥30.0: obesity) then the optimal weight gain is suggested for each group.^[23]

Statistical analysis

All statistical analyses were done using IBM SPSS Statistics software version 24 (IBM SPSS Statistics, Armonk, USA). The normality of the variables was assessed using the Kolmogorov–Smirnov test. The differences in variables between the study groups were tested using an independent sample *t*-test and a Chi-square test for parametric variables and categorical variables, respectively. To perform multivariate logistic regression, we regarded CA as a dependent variable. To control the possible confounding factors, and to identify independent risk factors for CA, multivariate logistic regression, adjusted odds ratios (ORs), and 95% confidence intervals (CIs) were carried out for this study. Those variables with a value of *P* value < 0.2 (parents' level of education, mother's age, parents' underlying illness, pregnancy care, birth weight, CA among first-grade relatives, folic acid and multivitamin intake in pregnancy, consumption of tea, pickles, barberry, and saffron in pregnancy) in univariate analysis were included in the backward step-wise model. *P* value < 0.05 was considered as statistically significant.

Results

The characteristics of the subjects in the control and CA groups have been shown in Table 1. A significant difference was detected between the study groups in terms of the mother's level of education (*P* = 0.024), mother's Age (*P* = 0.048), pregnancy care (*P* = 0.038), birth weight (*P* < 0.001), anemia in mother (*P* = 0.01), mother's underlying disease (*P* = 0.005), father's underlying disease (*P* = 0.047), and history of genetic disease and abnormality in the first-degree family (*P* < 0.001).

Table 2 summarizes the use of some herbal products, supplements, substances, and tobacco by mothers during pregnancy in the control and CA groups. The complete intake of multivitamins and folic acid supplements was significantly higher among the control group compared to the CA group (*P* < 0.05). However, weekly pickled vegetable consumption (more than 3 times), daily intake of tea (five cups and more), and daily intake of barberry fruit (more than a tablespoon) were significantly higher in the CA group compared to the control group (*P* < 0.05).

The analysis of risk factors associated with CA has been presented in Table 3. Mother's underlying disease (OR = 4.38; 95% CI: 1.13–16.97), history of genetic disease and abnormality in the first-degree family (OR = 18.28; 95% CI: 4.93–67.71), and birth weight (OR = 7.18; 95% CI: 2.17–23.79) were positively associated with the likelihood of CA. Incomplete and no intake of folic acid supplement was associated with increased risk of CA (OR = 2.63; 95% CI: 1.28–5.39, OR = 24.27; 95% CI: 5.10–115.43). Moreover, more than 3 times pickled vegetable consumption in a week was also associated with an increased risk of CA (OR = 5.09; 95% CI: 1.66–15.55). More daily intake of barberry (more than a tablespoon) was associated with higher odds of CA (OR = 9.23; 95% CI: 3.42–24.90). There was no significant association between CA and daily intake of saffron (*P* ≥ 0.05). Five and more than five cups of tea per day had a positive significant association with CA (OR = 3.21; 95% CI: 1.05–10.80).

Discussion

In the present study, we found that maternal more daily intake of barberry, more than 3 times pickled vegetable consumption in the week, five and more than five cups of tea consumption per day, incomplete and no intake of the folic acid supplement, mother's underlying disease, history of genetic disease and abnormality in the first-degree family, and birth weight were positively related to the odds of CA.

The findings of this study showed that more daily intake of barberry (*Berberis vulgaris*) in mothers was positively related to the odds of CA. Despite the beneficial impacts of barberry on various cell lines, some documents have shown the negative effects of it on humans and animals.^[24–26] Kamrani Rad *et al.*^[27] reviewed the toxicological effects of barberry and its active compound, berberine. According to their study, barberry and berberine could motivate gastrointestinal disturbance and ulceration, cardiotoxicity, neurotoxicity, phototoxicity immunotoxicity, and jaundice in a time and concentration-dependent manner. Berberine by increasing reactive oxygen species production, impeding adenine nucleotide translocase, apoptosis, and necrosis

Table 1: The characteristics of the subjects in the Control and CA groups

Variables	Control group (n=150)	CA group (n=150)	χ^2	P^a
Father's level of education (n) (%)				
Illiterate	9 (6)	12 (8)	7.09	0.069
Under diploma	109 (72.7)	118 (78.7)		
Diploma	4 (2.7)	7 (4.7)		
Academic	28 (18.7)	13 (8.7)		
Mother's level of education (n) (%)				
Illiterate	8 (5.3)	18 (12)	9.78	0.024
Under diploma	108 (72)	115 (76.7)		
Diploma	27 (18)	13 (8.7)		
Academic	7 (4.7)	4 (2.7)		
Familial Marriage (n) (%)				
First-grade relative	40 (26.7)	44 (29.3)	0.687	0.709
Second-grade relative	28 (18.7)	23 (15.3)		
Far relative/Not Related	82 (54.7)	83 (55.3)		
Mother's Age (n) (%)				
Under 18 years	6 (4)	2 (1.3)	5.90	0.048
Aged 18–35	117 (78)	106 (70.7)		
Over 35 years old	27 (18)	42 (28)		
Father's age (n) (%)				
Aged 18–35	102 (68)	92 (61.3)	1.45	0.227
Over 35 years old	48 (32)	58 (38.7)		
Pregnancy care				
Less than 6 times	66 (44)	84 (56)	4.32	0.038
6 times and more	84 (56)	66 (44)		
Birth weight (n) (%)				
<2500 g	145 (96.7)	121 (80.7)	19.10	<0.001
≥ 2500 g	5 (3.3)	29 (19.3)		
Parity (n) (%)				
First pregnancy	17 (11.3)	13 (8.7)	0.594	0.743
2 nd to 4 th pregnancy	41 (27.3)	42 (28)		
5 th or more	92 (61.3)	95 (63.3)		
Anemia in mother (n) (%)				
No	137 (98.6)	114 (91.9)	6.60	0.010
Yes	2 (1.4)	10 (8.1)		
Weight gain in pregnancy				
Met	105 (74.5)	99 (68.8)	1.15	0.285
Below and exceed	36 (25.5)	45 (31.3)		
Mother's underlying disease				
No	145 (96.7)	132 (88)	7.95	0.005
Yes	5 (3.3)	18 (12)		
Father's underlying disease				
No	147 (98)	140 (93.3)	3.94	0.047
Yes	3 (2)	10 (6.7)		
History of genetic disease and abnormality in first-degree family				
No	147 (98)	114 (76)	32.09	<0.001
Yes	3 (2)	36 (24)		

Data are frequency (percent) for qualitative variables. a: From Chi-square for qualitative variables. *P*-values of statistical significance (*P*<0.05) are presented in bold

pathways makes its toxicity on both normal and cancer cells in a dose-dependent manner. Moreover, a review by Prajwala *et al.*^[28] reported that berberine is probably safe for most adults for short-term consumption but it is unsafe for newborns, infants, pregnant and lactating women, and patients with diabetes, so the intake of this plant should be cautioned.

We observed that more than 3 times pickled vegetable consumption in the week was positively related to the odds of CA. Masinaei Nejad *et al.*^[16] in a case-control study revealed that the use of pickled vegetables during pregnancy has an association with CA. El Bilbeisi *et al.*^[29] in a cohort study concluded that the Asian-like dietary pattern may be associated with a lower prevalence of

Table 2: Maternal use of some herbal products, supplements, substances, and tobacco during pregnancy in the Control and CA groups

Variables	Control group (n=150)	CA group (n=150)	χ^2	<i>P</i> ^a
Folic acid consumption			34.2	<0.001
Complete	117 (78)	72 (28)		
Incomplete	29 (19.3)	50 (33.3)		
No	4 (2.7)	28 (18.7)		
Iron consumption			5.49	0.066
Complete	137 (91.3)	125 (83.3)		
Incomplete	11 (7.3)	17 (11.3)		
No	2 (1.3)	8 (5.3)		
Multivitamin consumption			6.48	0.039
Complete	137 (91.3)	123 (82)		
Incomplete	11 (7.3)	19 (12.7)		
No	2 (1.3)	8 (5.3)		
Weekly pickle consumption			9.15	0.002
3 times or less	144 (96)	129 (86)		
More than 3 times	6 (4)	21 (14)		
Daily intake of saffron			3.12	0.077
Less than 3 strands	147 (98)	141 (94)		
3 strands and more	3 (2)	9 (6)		
Daily intake of tea			9.01	0.011
Less than 2 cups	17 (11.3)	15 (10)		
2-5 cups	88 (58.7)	65 (43.3)		
5 cups and more	45 (30)	70 (46.7)		
Daily intake of barberry fruit			25.12	<0.001
One or fewer than a tablespoon	143 (95.3)	112 (74.7)		
More than tablespoon	7 (4.7)	38 (25.3)		
Daily intake of drugs			0.047	0.828
No	139 (92.7)	138 (92)		
Yes	11 (7.3)	12 (8)		
Substance abuse			0.094	0.759
No	145 (96.6)	144 (96)		
Yes	5 (3.4)	6 (4)		
Daily Tobacco use			0.680	0.409
No	148 (98.6)	146 (97.3)		
Yes	2 (1.4)	4 (2.7)		

Data are frequency (percent) for qualitative variables. ^aFrom Chi-square for qualitative variables. *P*-values of statistical significance (*P*<0.05) are presented in bold

preterm birth, low birth weight, and CA, whereas the Western dietary pattern may be associated with a higher prevalence of preterm birth. The significant association between maternal pickled vegetable consumption and CA may be due to increased sodium in the mother's body and its negative effect on fetal development. It was shown that high maternal salt consumption during pregnancy in bradykinin B2 receptor-deficient mice causes renal hypodysplasia.^[30]

Regarding the association of maternal saffron use in gestation with CA, we did not reach any significant association. More than 90% of the studied mothers consumed saffron less than 3 strands per day. It was shown that intake of saffron in doses higher than 5 g/kg induced several unfavorable effects such as abortion, nausea, and heart rate decrease in humans.^[31] Moallem *et al.*^[20] showed that the administration of the main

components of saffron, crocin, and safranal in pregnant mice disrupted the growth of fetuses and caused various fetal anomalies, certainly skeletal anomalies. The authors suggested that serious caution must be taken into account when saffron is consumed during gestation.

In the present study, five and more than five cups of tea consumption per day had a positive significant association with CA. It is shown that catechin, an antioxidant found in tea, can decrease intestinal absorption of folate by inhibiting the enzyme dihydrofolate reductase. This enzyme reduces the inactive form of folate to the active form and has a role in intestinal uptake of folate.^[32,33] Then intake of tea during pregnancy may pose pregnant women at risk due to its probable antifolate features. Consistent with our findings, some studies have found tea intake can increase the risk of neural tube defects (NTDs) among tea drinkers compared to nondrinkers.^[34-36] A

Table 3: The analysis of risk factors associated with congenital anomalies

Variate	Category	B	Adjusted OR	P	(95% CI)	
					Lower	Upper
Mother's underlying disease	No		1			
	Yes	1.47	4.38	0.03	1.13	16.97
History of genetic disease and abnormality in first-degree family	No		1			
	Yes	2.90	18.28	<0.001	4.93	67.71
Birth Weight	<2500 g		1			
	≥2500 g	1.97	7.18	0.001	2.17	23.79
Maternal folic acid intake	Complete		1			
	Incomplete	0.96	2.63	0.007	1.28	5.39
	No	3.18	24.27	<0.001	5.10	115.43
Maternal weekly pickles consumption	3 times or less		1			
	More than 3 times	1.62	5.09	0.004	1.66	15.55
Maternal daily intake of saffron	Less than 3 strands		1			
	3 strands and more	1.65	1.17	0.87	0.625	8.58
Maternal daily intake of barberry	One or fewer than a tablespoon		1			
	More than a tablespoon	2.22	9.23	<0.001	3.42	24.90
Maternal daily intake of tea	Less than 2 cups		1			
	2–5 cups	0.59	1.82	0.32	0.55	5.98
	5 cups and more	1.16	3.21	0.047	1.05	10.80

Those variables with a value of $P < 0.2$ (parents' level of education, mother's age, parents' underlying illness, pregnancy care, birth weight, CA among first-grade relatives, folic acid and multivitamin intake in pregnancy, consumption of tea, pickles, barberry and saffron in pregnancy) in univariate analysis were included in the backward step-wise model. P -values of statistical significance ($P < 0.05$) are presented in bold

cross-sectional study detected that daily consumption of ≥ 4 cups of green tea during pregnancy is related to low blood levels of folate.^[37] However, in contrast with our study, Yazdy *et al.*^[38] could not reach a significant association between tea consumption and spina bifida.

The results of the present study also confirm the association of some of the known factors including maternal incomplete and no intake of the folic acid supplement, mother's underlying disease, history of genetic disease and abnormality in the first-degree family, and birth weight with CA.

The results of the present study showed that about 72% of mothers in the CA group did not correctly use folic acid supplements, while 78% of mothers in the control group consumed them completely. Contrary to mandatory folic acid supplementation in Iran from 2004, folic acid intake in Iranian women is not optimal.^[39,40] Some factors influence the use of this supplement including the level of education, mother's age, awareness of folic acid, service equity and availability of health services, national health policies, and national socio-economic classification.^[41,42] Therefore, it is necessary to carry out educational interventions by health care providers to increase the awareness of mothers and consequently the consumption of folic acid supplements.^[43] Taking folic acid during the preconception and early stages of pregnancy is important in preventing CA such as NTDs, hydrocephalus, limb defects, oral facial clefts, pyloric stenosis, congenital heart disease, and urinary tract anomalies.^[44,45] In agreement with our findings,

Masoudi *et al.*^[39] also in a case-control study in the south of Iran observed that adequate intake of folic acid supplements before and during pregnancy can decrease the risk of NTDs. Moreover, a meta-analysis of case-control, cohort, and interventional studies has revealed that maternal folate supplementation has a significant association with a lowered congenital heart disease risk.^[46] Relation of the mother's underlying disease, history of genetic disease and abnormality in the first-degree family, and birth weight with CA is shown in previous studies.^[2,47-54]

Limitation and recommendation

The present study has some limitations. We could assess only living people with CA, and we could not evaluate severe anomalies that contributed to stillbirth, abortion, and death. Because the sample size was small, we could not evaluate the relationship between studied factors and CA types. Further detailed studies to determine the teratogenicity mechanism of these factors are recommended.

Conclusions

In the present study, we found that maternal use of barberry, pickled vegetables, and tea during pregnancy were positively related to the odds of CA. Further detailed studies to determine the teratogenicity mechanism of these factors are recommended. Moreover, the results of the present study also confirm the association of some of the known factors including maternal incomplete and no intake of the folic acid supplement, mother's underlying

disease, history of genetic disease and abnormality in the first-degree family, and birth weight with CA.

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Conflicts of interest

There are no conflicts of interest.

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