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Original Article

Factors Associated with Infant Mortality Due to Congenital Anomalies: A Population-Based Case-Control Study

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Abstract

Background: Congenital anomalies are one of the major public health problems and one of the leading cause of infant mortality and morbidity. We aimed to investigate some factors associated with infant mortality due to congenital anomalies in several provinces of Iran.

Methods: This case-control study was conducted on 2199 women referring health centers of nine provinces of Iran 2015-2018. Cases were defined as mothers with infant death due to congenital anomalies, and control group comprised of mothers with live birth or infant deaths due to other causes (n=1986). The descriptive data were expressed as percentage and frequency. Factors associated with infant death due to congenital anomalies were evaluated and analyzed at 95% confidence level by logistic regression analysis.

Results: The multiple logistic regression analysis reveal that history of cesarean delivery [OR:2.13 ;95%CI (1.58-2.87)], maternal age [OR:1.94 ;95%CI (1.31-2.86)])], area of living [OR: 1.69;95%CI (1.22-2.33)], maternal smoking during pregnancy [OR: 1.41; 95%CI (1.02-1.95)], consanguineous marriage [OR:1.53;95%CI (1.12-2.08)], also low birth weight [OR: 3.09; 95%CI (2.23-4.30)] were significantly associated with infant death due to congenital anomalies.

Conclusion: Identification of factors associated with congenital anomalies has been shown to reduce treatment costs and medical complications of neonates. Therefore, genetic counseling and educational programs for high-risk women, and prenatal screening are essential to identify and prevent factors contributing to congenital abnormalities.

Keywords: Congenital abnormalities; Infant mortality; Iran

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Introduction

Infant mortality rate (IMR) is one of the most important indicators of development of countries and it is also a good measure of community health and a representative of the extent to human development (1). Congenital anomalies (CA) are one of the major causes of infant death and causing 20% mortality rate among children (2). CA can be defined as structural or functional anomalies (malformations, deformations and disruptions) of genetic, environmental or unknown causes that occur during intrauterine life and can be detected during or after pregnancy (3).
The pattern of CA is different depending on the region and over time. Generally, congenital abnormalities CNS and the cardiovascular and musculoskeletal systems are most common (4). According to the WHO report in 2016, about 303,000 neonates die within the first 4 wk of life due to congenital defects throughout the world (5). The prevalence of these abnormalities significantly varies in Iran and all around the world. As such, the prevalence of CA is 1.7% in Brazil (6), 1.84% in India (7), and 6.2% in Iran (2). Variation in prevalence rates in different countries may be due to geographical, racial, social and economic differences (8). Although, about 40%–60% of CA causes are unknown various factors including genetic, environment, and teratogens such as maternal alcohol addiction, diabetes, malnutrition, infections, drug use, and exposure to chemical or radioactive substances are shown to contribute to CA (9). About 60% of birth defects can be prevented (10). Prevention strategies are considered as one of the most important indicators in reducing the prevalence of CA in several genetic counseling and training programs for high-risk individuals, and prenatal screening are essential to identify and prevent factors associated with CA (10, 11).
We aimed to investigate some factors associated with infant mortality due to congenital anomalies in several provinces of Iran.

Materials and Methods

The project was approved ethically and financially supported by Vice Chancellor of Research in Hormozgan and Shiraz Universities of Medical Sciences with registration numbers (No. 94113) and (No. 93-01-42-8964) respectively.
This study was a population-based case-control method on mothers who visit primary health care (PHC) units in Iran. Case group includes mothers who had infant death due to congenital anomalies. In the period 2015-2018, data were collected from public health care centers in 9 provinces.
In this study 2199 mothers from nine different regions of Iran who referred to healthcare centers were selected. The regions included Kohgiloyeh and Boyerahmad, Fars, Yazd, Hormozgan, Kermanshah, Golestan, Hamadan, Southern Khorasan and city of Mashhad. Participants included 1050 mothers had 1-59-month infant death, and 1149 mothers had 1-59 month live birth. Case group (n=213) was defined as mothers with infant death due to congenital anomalies, and control group (n=1986) comprised of mothers with 1-59 month live birth or infant deaths due to other causes (837 infant deaths due to other causes, and 1149 live births).
Multistage cluster sampling method was performed for obtaining sample from different parts of Iran. Geographical divisions of Iran were considered for this purpose. Nine clusters (provinces) were randomly selected in this stage. In the second stage, each of the clusters (provinces) were divided into five areas, north, south, east, west, and central. One city randomly selected from each of these areas. In the third stage, two health care centers (one urban and one rural health care center) were randomly selected. Ten self-administered checklists were filled by well-trained person according to an instruction in both rural an urban health care centers. If lower than ten cases were available in the center, the nearest center was selected for completing the

remaining checklists, and for the centers with more than ten cases, the checklists were filled from a random sample of mothers. In each center, the process of data gathering for both case and control groups was conducted on the same day. The most of control group were a random sample of mothers referring to the health care center in the time of data collection.

Considering maternal age higher than 35 yr as a risk factor, we arrived at a sample size of 200 cases for each study group (p0=0.3, p1=0.44, z0.95=2, z (1-β)=0.8).

The inclusion criteria in this survey were: mothers with 1-59 month infant death due to congenital anomalies for cases group, and mothers with no history of 1-59 infant death, or with no history of 1-59 month infant death due to congenital anomalies for control group.

The required data were extracted through face to face interviews with mothers and medical records documented in health centers. Data collection was conducted using a researcher-made questionnaire. The content validity of the questionnaire was approved by a group of experts, and the reliability was measured. The questionnaire comprised of data on demographic characteristics (e.g. mother's and father's age, area of living, ethnicity, infant's gender, and parental consanguinity), type of delivery, birth order, birth weight, positive urine cultures during pregnancy, maternal smoking during pregnancy, unwanted pregnancy, supplementation during pregnancy, multiple birth, maternal body mass index (BMI) during pregnancy, maternal hypertension, dysuria and gestational diabetes.

Statistical analysis

Mean (standard deviation) and frequency (percentage) were reported for quantitative and qualitative data, respectively. Univariate and multiple logistic regression analyses were done to determine the factors associated with infant mortality due to congenital anomalies. All of the variables with *P*-value than 0.2 were entered into the multiple model. Data were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA) with a significance level of 0.05.

Results

Results of univariate regression analysis include crude odds ratio for case and control groups presented in Table 1. Overall, 213 mothers as case group, and 1986 mothers, as control group were selected. The majority of the mothers in case group (16.5%) were 35 yr and older, 11.2% are rural and 10% had Fars ethnicity.

Results of univariate analysis revealed that type of delivery, maternal age, birth order, father's age, area of living, consanguineous marriage, maternal smoking, Unwanted pregnancy and birth weight were significantly associated with infant death due to congenital anomalies ($P<0.05$).

Table 1: Descriptive results of univariate logistic regression analysis of factors associated with infant death due to congenital anomalies

Variable	*Subgroup*	*No. (%)*		*Crude odds ratio (95% CI)*	*P-value*
		Case	Control		
Infant's gender	Girl	111 (9.4)	1073 (90.6)	Reference	-
	Boy	102 (10)	913 (90)	1.08 (0.81-1.43)	0.59
Type of delivery	Vaginal	116 (7.4)	1451 (92.6)	Reference	-
	Cesarean	97 (15.3)	535 (84.7)	2.27 (1.7-3.02)	<0.001
Birth order	First	68 (8)	781 (92)	Reference	-
	Second	62 (8.4)	672 (91.6)	1.06 (0.74-1.52)	0.75
	Third or more	83 (13.5)	533 (86.5)	1.79 (1.27-2.51)	0.001
Maternal age	<35 years	173 (8.8)	1783 (91.2)	Reference	-
	35 years and older	40 (16.5)	203 (83.5)	2.03 (1.39-2.95)	0.001

Father's age	<35 years	146 (8.9)	1499 (91.1)	Reference	-
	35 years and older	67 (12.1)	487 (87.9)	1.41 (1.04-1.92)	0.03
Area of living	Urban	58 (7.1)	759 (92.9)	Reference	-
	Rural	155 (11.2)	1227 (88.8)	1.65 (1.21-2.26)	0.002
Ethnicity	Fars	150 (10.0)	1356 (90.0)	1.30 (0.95-1.77)	0.09
	Other*	63 (8.1)	713 (91.9)	Reference	-
Parental consanguinity	Yes	77 (12.4)	546 (87.6)	1.56 (1.16-2.10)	0.003
	No	136 (8.2)	1523 (91.8)	Reference	-
Maternal smoking during pregnancy	Yes	152 (11.0)	1233 (89.0)	1.65 (1.20-2.25)	0.002
	No	61 (6.8)	836 (93.2)	Reference	-
Unwanted pregnancy	Yes	22 (13.8)	137 (86.2)	1.62 (1.01-2.61)	0.04
	No	191 (9.0)	1932 (91.0)	Reference	-
Supplementation	Yes	170 (9.0)	1717 (91.0)	0.81 (0.56-1.15)	0.24
	No	43 (10.9)	352 (89.1)	Reference	-
Multiple births	Yes	7 (8.8)	73 (91.3)	0.92 (0.42-2.04)	0.85
	No	206 (9.4)	1996 (90.6)	Reference	-
Maternal BMI during pregnancy	Under weight	2 (10.5)	17 (89.5)	Reference	-
	Normal	63 (11.8)	472 (88.2)	0.88 (0.19-3.90)	0.86
	Overweight	93 (7.9)	1079 (92.1)	1.36 (0.31-5.99)	0.68
	Obese	55 (9.9)	501 (90.1)	1.07 (0.24-4.76)	0.92
Maternal hypertension	Yes	5 (7.8)	59 (92.2)	0.81 (0.32-2.06)	0.67
	No	208 (9.4)	2010 (90.6)	Reference	-
Maternal dysuria	Yes	27 (8.1)	306 (91.9)	0.83 (0.54-1.27)	0.40
	No	186 (9.5)	1763 (90.5)	Reference	-
Positive urine cultures	Yes	31 (10.8)	257 (89.2)	1.02 (0.67-1.55)	0.90
	No	153 (9.6)	1453 (90.4)	Reference	-
	Unknown	29 (9.4)	279 (90.6)	0.88 (0.58-1.33)	0.55
Maternal diabetes	Yes	7 (9.1)	70 (90.9)	0.97 (0.44-2.13)	0.94
	No	206 (9.3)	1999 (90.7)	Reference	-
Infant birth weight	<2500g	68 (21.9)	242 (78.1)	0.28 (0.20-0.38)	<0.001
	2500-4000g	142 (7.3)	1790 (92.7)	Reference	-
	>4000g	3 (7.5)	37 (92.5)	0.97 (0.29-3.21)	0.97

*Kurd, Lur, Baluch

Factors associated with infant death due to congenital anomalies by multiple logistic regression are shown in Table 2. The odds of infant death due to congenital anomalies was 2.13 times higher in mothers with cesarean delivery [OR:2.13 ;95%CI (1.58-2.87)]. Moreover, the odds of infant death due to congenital anomalies was shown to be 1.94 times higher in mothers aged 35 and older [OR:1.94 ;95%CI (1.31-2.86)])]. Moreover, mothers who living in rural areas had a higher odds of infant death than those living in urban areas [OR: 1.69;95%CI (1.22-2.33)]. Maternal smoking during pregnancy was shown to increase the risk of infant death due to congenital anomalies by 1.41 times [OR: 1.41; 95%CI (1.02-1.95)]. Consanguineous marriage increased the risk of infant death due to congenital anomalies by 1.53 times [OR:1.53;95%CI (1.12-2.08)]. Finally, infant with birth weight<2500g were 3.09 times more likely to die due to congenital anomalies [OR: 3.09; 95%CI (2.23-4.30)].

Table 2: Outcomes of multiple logistic regression analysis of factors associated with infant death due to congenital anomalies adjusted for father's age, Unwanted pregnancy and birth order

Variable	*Subgroup*	*Adjusted odds ratio (95%CI)*	*P-value*
Type of delivery	Vaginal	Reference	-
	Cesarean	2.13 (1.58-2.87)	0.001
Maternal age	<35 years	Reference	-
	35 years and older	1.94 (1.31-2.86)	0.001
Area of living	Urban	Reference	-
	Rural	1.69 (1.22-2.33)	0.001
Parental consanguinity	Yes	1.53 (1.12-2.08)	0.006
	No	Reference	-
Maternal smoking during pregnancy	Yes	1.41 (1.02-1.95)	0.03
	No	Reference	-
Infant birth weight	<2500g	3.09 (2.23-4.30)	0.001
	2500-4000g	Reference	-
	>4000g	3.28 (0.96-11.17)	0.05

Discussion

Type of delivery, maternal age, area of living, maternal smoking during pregnancy, consanguineous marriage, and birth weight were significantly associated with infant death due to congenital anomalies.

The odds of infant death due to congenital anomalies was shown higher at mothers with history of cesarean, as mothers with history of cesarean were 2.13 times more likely than those with normal delivery to have infant death due to congenital anomalies, which was in accordance with previous studies (12). However, these results were inconsistent with results of some studies (13), attributed to inappropriate condition of fetus in uterus in cesarean section (12).

Another result of our study showing that the risk of infant death due to congenital anomalies is higher in mothers aged older than 35 years. Higher rate of birth defects in mothers at older ages can be attributed to higher rates of maternal health problems at older ages or socioeconomic factors (4, 14). Maternal age is known as the most important non-genetic factor for chromosomal abnormalities in the fetus. Accordingly, advanced maternal age increased the risk of having a child with congenital anomalies. As the age increases, the probability of an ovulation malfunction is increased. These errors may result in the absence of chromosomes leading to creation of various chromosomal abnormalities and syndromes (4, 15).

Moreover, infant death due to congenital anomalies was more prevalent in women living in rural areas than in urban areas, which was in line with some previous studies (14, 16, 17) and inconsistent with some other studies (6, 13). Increased prevalence of infant death due to congenital anomalies in urban areas may be due to more exposure to air pollution, hazardous factors in parent's workplace, and consumption of fast food. On the other hand, lack of healthcare facilities for mothers during pregnancy, and low socioeconomic status increased the rate of congenital anomalies in rural areas (14, 16).

According to our study, the risk of birth defects is 1.5 times higher in consanguineous marriages. Consanguineous marriage has been shown as a major risk factor for congenital anomalies, which was predictable with results of studies on the relationship between genetic factors and congenital anomalies (13, 18, 19). The contradiction in these results may be due to different calculated risk ratio in various studies, or differences in prevalence of consanguineous marriage in various regions of the world. Hence, premarital counseling about genetic counseling play a key role in the prevention of congenital anomalies among infants (18).

Results of our study indicate that the risk of infant death due to congenital anomalies was significantly associated with maternal smoking during pregnancy. Previous studies have shown maternal smoking as a teratogen (15, 20). Anomalies happen due to the effects of carbon monoxide. It releases the hormones that cause vasoconstriction in the uterus and placenta by reducing tissue oxygenation and nicotine, so it carries less oxygen and fewer nutrients to the fetus (15).

In addition, birth weight was shown to be significantly associated with neonatal congenital abnormalities. The congenital anomalies was positively associated with low birth weight (LBW) (13, 21). However, in Uganda, no significant relationship was found between birth weight and prevalence of congenital anomalies (22). The underlying mechanism of the association with LBW is unknown but may be explained either by a shared pathogenesis or relative lack of androgen inducing hormones (human chorionic gonadotropin) affecting smaller fetuses (23). Some events such as cerebral palsy, mental retardation and cognitive dysfunctions are generally higher in LBW infants than in infants with natural birth weight (24).

Conclusion

Type of delivery, maternal age, area of living, maternal smoking during pregnancy, consanguineous marriage, and birth weight were significantly associated with infant death due to congenital anomalies. Identification of factors associated with congenital anomalies has been shown to reduce treatment costs and medical complications of neonates. Hence, genetic counseling and educational programs for high-risk women, and prenatal screening are essential to identify and prevent factors contributing to congenital abnormalities.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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