Evaluating the association between neonatal mortality and maternal high blood pressure, heart disease and gestational diabetes: A case control study

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Background: Prevention of noncommunicable diseases (NCDs) during pregnancy is recommended due to severe complications for mothers and infants. Considering that NCDs have a significant impact on infant mortality, this study was conducted to investigate the relationship between mothers' underlying diseases and gestational diabetes and infant mortality in Iran. **Materials and Methods:** Mothers who referred to the health centers in nine provinces of Iran were included. This case–control study used data collected from pregnant women. There were 1162 cases and 1624 controls. The required data were collected from mothers' health records and through interviews. **Results:** The chances of neonatal mortality in women with a body mass index (BMI) of 30–35, 1.7 times (odds ratio [OR] = 1.7, confidence interval [CI]: 1.19–2.44, P = 0.003) was higher compared with women with a normal BMI. The chance of neonatal mortality among mothers with high blood pressure was three times higher compared with healthy mothers (OR = 3.04, 95% CI: 1.98–4.65, P < 0.001). The chance of neonatal mortality in women with kidney disease was also 1.64 times higher than mothers without kidney problems (OR = 1.64, 95% CI: 1.1–2.45, P = 0.015). In the study of gestational diabetes, the chance of neonatal mortality among the mothers who had at risk was 1.63 times higher than mothers without gestational diabetes (OR = 1.63, 95% CI: 0.84–3.16, P = 0.014). Furthermore, the chance of neonatal mortality among the mothers who had heart disease was 1.10 times higher than mothers without heart disease (OR = 2.10, 95% CI: 0.88–4.99, P = 0.014). **Conclusion:** This study showed that undiagnosed underlying diseases were related to neonatal mortality, which highlights the importance of caring for and counseling about the underlying diseases, screening, and controlling blood sugar levels before and during pregnancy to prevent infant mortality by all means possible.

Key words: Gestational diabetes, high blood pressure (hypertension), kidney disease, neonatal mortality

INTRODUCTION

Noncommunicable diseases (NCDs) are one of the causes of increased rates (68%) of morbidity and mortality worldwide.[1] On the other hand, the prevalence of gestational diabetes mellitus (GDM) in North America, South America, Africa, Middle East and North Africa, Europe, South East Asia, and Western Pacific is 7.0%,

Access this article online

Quick Response Code:	**Website:** www.jmsjournal.net
	DOI: 10.4103/jrms.JRMS_814_18

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11.2%, 8.9%, 11.7%, 5.8%, 12.9% and 11.7% respectively.[2] GDM defined as any degree of glucose intolerance diagnosed that occurs for the first time in a woman during pregnancy,[3] which include multiple complications such as macrosomia, congenital malformations, hyaline membrane disease, fetal malnutrition, infection, and poisoning. This is the leading causes of neonatal mortality, prematurity, cesarean birth, urgent need for hospitalization in the neonatal intensive care unit, and death during childbirth.[4]

Hypertension is also a serious condition. The prevalence of gestational hypertensive disorders in Iran among 25–65-year-old women was estimated as 6%.[5] Several studies have shown that pregnancy-induced hypertension occurs in 10%–16% of all, which is a significant cause of maternal and neonatal morbidity and mortality such as nulliparity, advanced age, diabetes, twinning, and smoking associated with hypertensive disorders in women.[6-8]

Furthermore, kidney disease is another NCD. The overall global prevalence of chronic kidney diseases and Iran was 13·4% and 11.68%, respectively, which include multiple complications such as preeclampsia, prematurity, dysfunctional labor, cesarean birth, and Apgar score of <7 compared without chronic kidney diseases.[9,10]

To evaluate the prevention and control of diseases and thus prevention of neonatal mortality, we require precise data to investigate the role of each one of NCDs in neonatal mortality. Therefore, this study was designed and conducted to examine the association between underlying diseases and gestational diabetes and neonatal mortality.

MATERIALS AND METHODS

Data collection
In this case–control study, required data have been collected using questionnaires, interviews, and family medical records of mothers who referred to the health centers in nine provinces of Iran including Fars, Hormozgan, Kermanshah, Hamedan, Kohgiluyeh and Boyer-Ahmad, Yazd, Khorasan, Golestan, and the city of Mashhad. Collected data through interviews with mothers included personal information of parents (maternal age, parental education, and ethnicity) and information on pregnancy (smoking) while data obtained from the health records included maternal prepregnancy weight, last weight measured before delivery, maternal height, maternal age during pregnancy, underlying diseases, and gestational diabetes.

Study population
In this study, to determine the sample size using the equation for detecting a difference between two proportions considering the design effect and the number of variables in the model, a sample size of 1150 participants in each group calculated. During the conduct of the study, considering the cooperation of the various health centers in different provinces, and to increase the accuracy of the study, a sample size of 2786 participants was determined which consisted of 1162 cases and 1624 controls.

Generally, glucose tolerance test (GTT) is being used in Iran to diagnose gestational diabetes among pregnant women. In this study, pregnant women are divided into four groups according to the GTT. The first group included women diagnosed with gestational diabetes. The second group consisted of women who did not have diagnosed or suspected with gestational diabetes. The third was at-risk group who have diagnosed just need to be monitored closely. According to the World Health Organization, the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period specified.[11]

Sampling
The samples of the study selected from nine provinces based on the geographic location and four cities chosen from each province (separately from north, south, east, and west). Next, an urban center and a rural center were selected out of the healthcare centers of these cities, and the required data were collected using questionnaires. In Iran, rural health centers based in the villages cover and support the health house of the village and often health houses in the several neighboring villages. This center has a population of about 9000 people and general practitioners, holders of associate degree and bachelor's degree in healthcare, and holders of associate degree and bachelor's degree in midwifery work in it. The primary responsibility of the center is to support the health houses, to monitor their performance, to accept the referrals, and to communicate appropriately with higher levels. However, urban healthcare centers are located in urban areas and support the health posts, general practitioners, holders of associate degree and bachelor's degree in healthcare, and holders of associate degree and bachelor's degree in midwifery work in this center as well. The center covers a smaller population (12,500 people), and it conducts all laboratory, radiology, and medical activities. The information related to all covered households includes information on the mother's status before, during, and after pregnancy maintained in family health records in these centers. Since the healthcare centers' professionals considered the closest care line in Iran, the relevant questionnaires distributed among them and the required data were collected by the shared and coordinated instruction by reviewing the participants' files. The judgment of some experts confirmed the validity of the questionnaire, and its reliability confirmed through a pilot study conducted with 50 mothers in Kermanshah (Cronbach's alpha = 0.66).

Data analysis

Collected data were entered in Excel, and after some intended corrections and elimination of incomplete questionnaires, data were entered into SPSS version 22.0 and the statistical analysis was performed as follows. Therefore, the results for the quantitative variables were reported in mean ± standard deviation format and the ordinal qualitative variables were reported in frequency and percentages. In univariate analysis, the relationship between variables and the dependent variable measured separately, and the results were reported based on the significant level for the given test (*P* value). Thus, to control the confounding effect of some variables, a multivariate logistic regression model was used. As a result, all the variables with a *P* < 0.3 entered into the regression model. Then, the hypothesis test was considered statistically significant with values (*P* value) <0.05. Since recall bias is the primary concern in case–control studies, this study sought to fix this problem as far as possible by selecting external variables with high recall ability and fewer recall errors.

RESULTS

Table 1 shows demographic characteristics, underlying maternal diseases, and gestational diabetes of participants in the study separately for controls and cases.

The results of univariate logistic regression analysis showed that there was a significant association between ethnicity, body mass index (BMI), education level, maternal age, hypertension, gestational diabetes, kidney disease and heart disease, and neonatal mortality (*P* < 0.05) [Table 2].

Multivariate logistic regression analysis showed that the chance of neonatal mortality among Kurds 2.56 times (odds ratio [OR] = 2.56, 95% confidence interval [CI]: 1.31–5.01, *P* = 0.006), among Baluchis 0.29 times (OR = 0.29, 95% CI: 0.183–0.471, *P* < 0.001), and among Turkmens 0.43 times (OR = 0.43, 95% CI: 0.24–0.76, *P* = 0.004) was higher compared with Fars ethnic group. The chance of neonatal mortality among illiterate mothers 2.61 times (OR = 2.61, 95% CI = 1.56–4.37, *P* < 0.001), elementary school graduates 2.6 times (OR = 2.6, 95% CI: 1.84–3.66, *P* < 0.001), secondary school graduates 2.64 times (OR = 2.64, 95% CI: 1.89–3.68, *P* < 0.001), and high school graduates 1.84 times (OR = 1.84, 95% CI: 1.35–2.51, *P* < 0.001) was higher compared with mothers with university degrees. The chances of neonatal mortality in women with a BMI under 19, 1.43 times (OR = 1.43, 95% CI: 1.12–1.81, *P* = 0.003), women with a BMI of 30–35, 1.7 times (OR = 1.7, CI: 1.19–2.44, *P* = 0.003) was higher compared with women with a normal BMI. The chances of neonatal mortality in mothers with high blood pressure were almost three times higher compared

Table 1: Demographic characteristics and underlying diseases of the mothers in two groups of cases and controls

Variable	Groups	Controls (*n*)	Cases (*n*)
Ethnic	Fars	1019 (63.8)	741 (65.7)
	Lor	108 (6.8)	77 (6.8)
	Turk	250 (15.7)	170 (15.1)
	Kurd	16 (1)	39 (3.5)
	Arab	16 (1)	14 (1.2)
	Baloch	101 (6.3)	40 (3.5)
	Turkoman	62 (3.9)	23 (2)
	Other	25 (1.6)	23 (2)
	Total	1597 (100)	1127 (100)
Maternal education	Illiterate	68 (4.2)	62 (5.4)
	Primary school	315 (19.4)	280 (24.2)
	Guidance school	347 (21.3)	309 (26.7)
	High school	648 (39.9)	413 (35.7)
	College	246 (15.1)	94 (8.1)
	Total	1624 (100)	1158 (100)
BMI	<19	242 (16.2)	239 (22.7)
	19-25	821 (54.8)	508 (48.2)
	25-30	323 (21.6)	204 (19.4)
	30-35	84 (5.6)	89 (8.5)
	>35	27 (1.8)	13 (1.2)
	Total	1497 (100)	1053 (100)
Maternal age	<35	1514 (94)	1035 (90)
	>35	97 (6)	115 (10)
	Total	1611 (100)	1150 (100)
Hypertension	Yes	47 (2.8)	44 (7.8)
	No	1579 (97.2)	1104 (92.2)
	Total	1626 (100)	1148 (100)
GDM	Without GDM	1353 (93.18)	802 (90.11)
	With GDM	79 (5.44)	63 (7.07)
	At risk GDM	20 (1.37)	25 (2.81)
	Total	1452 (100)	890 (100)
Kidney disease	Yes	75 (4.6)	74 (6.4)
	No	1551 (95.4)	1074 (93.6)
	Total	1626 (100)	1148 (100)
Smoking	Yes	83 (5.2)	55 (4.8)
	No	1525 (94.8)	1097 (95.2)
	Total	1608 (100)	1152 (100)
Heart disease	Yes	11 (0.7)	17 (1.5)
	No	1615 (99.3)	1130 (98.5)
	Total	1626 (100)	1147 (100)

GDM=Gestational diabetes; BMI=Body mass index

with healthy mothers (OR = 3.04, 95% CI: 1.98–4.65, *P* < 0.001). In the study of gestational diabetes, the chance of neonatal mortality among the mothers who had at risk was 1.63 times higher than mothers without gestational diabetes (OR = 1.63, 95% CI: 0.84–3.16, *P* = 0.014). Furthermore, chance of neonatal mortality among the mothers who had heart disease was 1.10 times higher than mothers without heart disease (OR = 2.10, 95% CI: 0.88–4.99, *P* = 0.014). Moreover, the chance of neonatal mortality in women with kidney disease was also 1.64 times greater than mothers without kidney disease (OR = 1.64, 95% CI: 1.1–2.45, *P* = 0.015).

Table 2: Estimation of crude and adjusted chance of neonatal mortality according to different variables of participating mothers

Parameter	Crude			Adjusted		
	OR	95% CI	*P*	OR	95% CI	*P*
Maternal age						
35>	1	-	-	1	-	-
>35	1.73	1.30-2.29	0.001			
Maternal education level						
Illiterate	2.38	1.57-3.62	0.001	2.61	1.56-4.37	0.001
Primary school	2.32	1.74-3.10	0.001	2.60	1.84-3.66	0.001
Middle school	2.33	1.75-3.09	0.001	2.64	1.89-3.68	0.001
High school	1.66	1.27-2.18	0.001	1.84	1.35-2.51	0.001
University graduate	1	-	-	1	-	-
Ethnic						
Fars	-	-	-	1	-	-
Lor	0.98	0.72-1.33	0.901	0.96	0.67-1.38	0.830
Turk	0.93	0.75-1.16	0.544	0.80	0.62-1.04	0.101
Kurd	3.35	1.85-6.04	0.0001	2.56	1.31-5.01	0.006
Arab	1.20	0.58-2.48	0.616	1.34	0.58-3.11	0.487
Baloch	0.54	0.37-0.79	0.002	0.29	0.18-0.47	0.001
Turkoman	0.51	0.31-0.83	0.007	0.43	0.24-0.76	0.004
Other	1.26	0.71-2.24	0.422	0.94	0.46-1.94	0.887
Hypertension						
No	1	-	-	1	-	-
Yes	2.92	2.03-4.20	0.0001	3.04	1.98-4.65	0.0001
Kidney disease						
No	1	-	-	1	-	-
Yes	1.42	1.02-1.98	0.036	1.64	1.10-2.45	0.015
Heart disease						
No	1	-	-	1	-	-
Yes	2.20	1.03-4.73	0.042	2.10	0.88-4.99	0.091
BMI						
19-25	1	-	-	1	-	-
<19	1.59	1.29-1.96	0.0001	1.43	1.12-1.81	0.003
25-30	1.02	0.83-1.25	0.846	0.95	0.75-1.20	0.670
30-35	1.71	1.24-2.35	0.001	1.70	1.19-2.44	0.003
>35	0.77	0.39-1.52	0.464	0.73	0.33-1.62	0.449
Smoking						
Yes	1	-	-	1	-	-
No	0.92	0.64-1.30	0.640			
Gestational diabetes						
No	1	-	-	1	-	-
Yes	1.34	0.95-1.89	0.089	1.23	0.82-1.85	0.313
At risk	2.10	1.16-3.82	0.014	1.63	0.84-3.16	0.148

BMI=Body mass index; OR=Odds ratio; CI=Confidence interval

DISCUSSION

The findings showed that the chances of neonatal mortality among mothers who had never undergone diabetes-screening tests during pregnancy were higher than mothers without gestational diabetes. Therefore, it can be said that the time of diagnosing GDM has a significant impact on the incidence of neonatal outcomes so that León *et al*. indicated that diagnosis of gestational diabetes after week 20 of pregnancy in 75.6% of the cases would lead to neonatal macrosomia followed by neonatal death.[12] Szymańska *et al*. showed a lower rate of neonatal macrosomia once GDM diagnosed in 24–28 weeks of pregnancy, compared with the diagnosis of GDM in later weeks, which would be followed by a reduced rate of neonatal mortality as well.[13] According to the results, it can be said that women with GDM who had never undergone diabetes-screening tests during pregnancy would remain undiagnosed, and thus, their blood sugar level would not be controlled and maintained at natural levels. As a result, the chance of neonatal mortality among these mothers was high.

According to the findings of the present study, no significant association found between gestational diabetes and neonatal mortality, which was consistent with the results of other studies.[14] Ahkter *et al.* showed that adverse outcomes would be reduced in mothers with good diabetic control.[15] In a study by Dunne *et al.* on 182 pregnant women with type 2 diabetes, 88% of women had healthy infants, and only 1.2% of them experienced infant mortality.[16] Another study by Maresh in 2001 showed that the incidence of gestational diabetes might lead to adverse maternal, fetal, or neonatal outcomes.[17] Furthermore, a study conducted by Persson and Hanson showed that gestational diabetes increases the risk of congenital disabilities and perinatal mortality in women,[18] which contradicts the findings of this study. Probably this is related to different design and sample size of the studies. Therefore, it can be said that considering the results of different studies, identification of diabetic mothers and diagnosis of gestational diabetes would result in a good blood sugar control both before and during pregnancy and would also lead to improved perinatal outcomes and reduced rate of preterm birth and neonatal mortality.

According to the findings of the study, the chance of neonatal mortality in mothers with higher blood pressure is higher than healthy mothers, which is consistent with the results of other studies as well.[19] Therefore, screening blood pressure among women of reproductive age and regular control of blood pressure during pregnancy play a significant role in reducing the consequences of this disease for pregnant women. The results also indicated that the chance of neonatal mortality among mothers with kidney diseases is higher than other women, which is consistent with the findings of another study.[20]

Fischer argued that women with moderate-to-severe chronic kidney diseases experience an increased rate of premature birth, low birth weight, and neonatal mortality compared with mothers with mild chronic kidney disease.[20]

Hou also showed that the infants survived in 70%–100% of pregnancies in women diagnosed with kidney failure or renal-transplant recipients; however, the rate of survival was 50% among women who became pregnant after starting dialysis.[21] The results of this study and other mentioned studies indicate the importance of diagnosis of kidney diseases in pregnant women so that, with early detection and control of the disease before or during neonatal pregnancy, mortality can be avoided to a large extent.

The rate of mortality in infants of mothers with a BMI between 30 and 35 was 1.7 times more than infants of women who had normal BMI. Similar findings obtained in studies conducted by Kristensen *et al.* in Scandinavia

(OR = 2.7)[22] and by Heude *et al.* (OR = 2.7).[23] However, contrary to the results of this study, in a study by Khashan and Kenny, no significant association was found between neonatal mortality and maternal obesity,[24] which may due to different design and sample size of the study.

The results of our study and other studies illustrate the importance of obesity among pregnant women. They also emphasize that obesity alone in the absence of gestational diabetes can be considered as a risk factor for neonatal mortality. Therefore, gestational diabetes and obesity are two risk factors associated with neonatal mortality. Thus, the necessary training for a weight loss and achieving a healthy weight, proper diet, and receiving counseling during pregnancy is required.

Moreover, in this study, the rate of neonatal mortality among infants of the mothers who had a BMI below 19 was higher than the infants of mothers with a healthy BMI. Similarly, in another study, Heude *et al.* argued that inadequate weight gain in pregnancy might indicate a nutrient deficiency, absence of expansion of plasma volume, infection, or other unknown problems, which can result in premature birth or small for gestational age (SGA) infants or lead to newborn infant death.[23] As a result, in addition to obesity, thinness also is important among pregnant women because it can cause premature birth, low birth weight followed by neonatal mortality; hence, necessary training about weight gain to reach a healthy weight, proper diet, and receiving counseling also required during pregnancy.

In univariate analysis, there was a significant relationship between maternal age over 35 years and neonatal mortality. However, this association was not significant in the multivariate analysis, which indicates the confounding role of age in this study, because older people would develop a variety of diseases and probably the diseases would be the leading cause of neonatal mortality, not the maternal age. The results of the present study also confirm this fact.[25]

In this study, the chance of neonatal mortality among Kurds, Baluchis, and Turkmens was significant, which was consistent with the results of other studies on ethnicity. Some studies conducted in Iran indicated that the rate of preterm birth is higher among Turkmens while the rate of hard labor is higher among Sistani's or Baluchis, and these two factors could be the leading causes of neonatal mortality. This contradiction could be due to under-reporting considering that Zahedan ranked last among provinces of Iran regarding access to healthcare indicators;[26] hence, a large number of infant deaths happened at home might not have been reported.

According to the findings of the study, the chance of neonatal mortality among mothers with low levels of education is

higher than among university-educated mothers, which is consistent with the results of other studies. In a study by Shirvani and Khosroshahi conducted in Tehran, a meaningful relationship found between neonatal mortality and under-education (below high school diploma).[27] In another study, Peña *et al*. showed that there has been a gradual reduction in the rate of neonatal mortality from 65/1000 newborns in illiterate mothers to 30/1000 newborns among educated mothers.[28] Considering that mothers with higher education levels have more information about health care during pregnancy than those with lower levels of education, it would be required to build a material culture to increase literacy levels among women. Furthermore, educating all under-educated women on health care during pregnancy is necessary.

There was no significant association between smoking and neonatal mortality in our study. It may be because smoking in Iranian women is not accepted; moreover, since, in our study, the questions about smoking were asked directly from the mother through interviews, many smoking mothers might not have reported it which increases the possibility of biased reporting in this area. Therefore, in future studies, the questions about smoking are required to be asked indirectly so that the underlying effects of cigarette smoking would be measurable.

In our study, no statistically significant association was found between maternal heart disease and neonatal mortality; however, a significant chance (2.1) was obtained in the study showing that since the number of pregnant women with heart disease was minimal in the present study, this insignificant relationship was the result of the small sample size of this study. In contrast to our study, other studies have found a significant association between this disease and neonatal mortality. Avila *et al*. in a study showed that the maternal mortality rate among pregnant women with heart disease was 2.7% and 0.13% of their infants being born preterm.[29] A study by Khairy *et al*. showed that adverse neonatal outcomes have occurred among 27.8% of women with heart disease including preterm birth (20.8%), being SGA (8.3%), respiratory distress syndrome (8.3%), intraventricular hemorrhage (1.4%), intrauterine fetal death (2.8%), and neonatal mortality (1.4%).[30]

Strengths and weaknesses of the study
The large sample size and sampling from various provinces are the strengths of the studies making it possible to generalize the results to the population of Iran. Using registered data in health records is one of the weaknesses of the study, and since that these data were not recorded for research purposes, some required data such as smoking by mothers were incomplete and because some cultural restrictions people refused to answer the related questions.

CONCLUSION

This study showed that underlying diseases, obesity, thinness, and undiagnosed diabetes in pregnant women might have significant effects on neonatal mortality. Therefore, these results highlight the importance of pregnancy care and counseling on underlying diseases, healthy weight, and monitoring blood glucose levels before and during pregnancy to prevent neonatal morbidity and mortality by all means possible. Accordingly, a screening program for underlying diseases, obesity, and thinness for high-risk group's as well as educational programs for women of reproductive age in these fields seem necessary.

Conflicts of interest
There are no conflicts of interest.

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