

# Consanguinity and Neonatal Death: A Nested Case-Control Study

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Received June 2014; Revised and accepted September 2014

## Abstract

**Objective:** Although numerous studies have found higher rates of abortion and still births following consanguinity (familial marriages), the question of whether consanguinity significantly increases the risk of neonatal death has inadequately been addressed. This study aims to evaluate familial marriage effects on neonatal death in rural areas in Iran.

**Materials and methods:** In this nested case-control study, 6900 newborns who were born in rural areas of Kohgiluyeh and Boyer-Ahmad Province (South-West of Iran) were followed till the end of neonatal period, and neonatal death was the outcome of interest. Subsequently 97 cases and 97 controls were selected in study cohort by using risk set sampling model. Crude and adjusted odds ratios (OR) were estimated by using a conditional logistic regression model.

**Results:** In the final model, prematurity (OR = 5.57), low birthweight (LBW) (OR = 7.68), consanguinity (first cousins) (OR = 5.23), C-section (OR = 7.27), birth rank more than 3 (OR = 6.95) and birth interval less than 24 months (OR = 4.65) showed significant statistical association with neonatal mortality ( $p < 0.05$ ).

**Conclusion:** According to our findings, after adjusting the effects of other significant risk factors, familial marriage to first cousins is considered as an important risk factor for neonatal death.

**Keywords:** Neonatal Death, Nested Case-Control Study, Consanguinity, Rural Areas, Iran

## Introduction

Neonatal mortality rate is one of the most important

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indicators for the evaluation of children health status and improvement of this health indicator is quite gradual in rural areas of Iran (1). Consanguinity or inbreeding is defined as familial marriages and it is categorized as 'close consanguinity' or 'first cousins' and 'remote consanguinity' or 'second cousins' or '

distant relative marriages' (2-4). Several studies have shown deleterious effects of consanguineous marriages on abortion, still births, neonatal deaths and infant mortalities (5-10). In several studies, consanguineous marriage has been reported as the most significant cause of genetically associated mortalities and related-by-blood couples were more likely to experience offspring death than non-familial couples (11,12). A research in Pakistan found that first cousin marriages were more prone to experience a child's death, compared to not-related-by-blood couples (13). Another study demonstrated a correlation between the genetic effect of consanguinity and offspring death among first cousin marriages after controlling for the non-genetic related factors (14).

In assessing the effects of consanguinity on neonatal and infant death, it is clearly accepted that variables such as maternal education, maternal age, birth intervals, gestational age and birth weight need to be adequately controlled (4).

Although numerous studies have found higher rates of abortion and still births following consanguineous marriages, for countries such as Iran the question of whether consanguinity significantly increased the risk of neonatal death is inadequately addressed. This study was done to give an evidence-based answer to this question and to provide a better evaluation of familial marriage effects on neonatal death in rural areas in Iran. To achieve this aim, we tried to use a sophisticated design as well as modern analytic techniques.

## Materials and methods

This research was carried out as a nested case-control study and the study cohort included all of the neonates born during 12 months in rural areas of Kohgiluyeh and Boyer-Ahmad province which is located in South-West of Iran. All of the cohort subjects were followed during the first 28 days of life and the outcome of interest was the neonatal death. For each case at the time of death, one control was randomly selected among all newborns with same birth date. According to the risk set sampling method, 97 controls were selected due to occurrence of 97 cases of neonatal death in the 6900 studied cohort. The sample size was enough to establish regression method analysis, based on general rule of 5-10 subjects per variable in each comparison group.

The dependent variable was neonatal death and the independent variables were parents relation (first cousins vs. remote consanguinity and non-familial marriages), gender (male vs. female),

gestational age (<37 weeks vs. ≥37 weeks), birth weight (<2500gr vs. ≥2500gr), maternal age (<18 or >35 vs. ≥18 or ≤35), birth rank (>3 vs. ≤3), delivery route (C-section vs. normal vaginal delivery (NVD)) and birth spacing (<24 months vs. ≥24 months). The data were analyzed using univariate and multivariate conditional logistic regression methods in Stata software (Stata Corp, USA) version 10.

## Results

Based on descriptive results, there are moderate discrepancies in frequencies of consanguineous marriages between the two groups (Table 1). Comparing the two groups, great differences are seen between LBW, prematurity, delivery type (C-section) and birth rank more than 3 of the two groups (Table 1). Univariate conditional logistic regression was performed to estimate crude ORs (Table 1).

In the next step, each risk factor with marked association ( $p$  value < 0.2) was selected for multivariate analysis. Thus, conditional logistic regression model included the birth weight (OR = 9.8, 95% CI = 3.90-24.60), gestational age (OR = 8.8, 95% CI = 3.50-22.20), parents relation (OR = 1.5, 95% CI = 0.84-2.95), births spacing (OR = 1.79, 95% CI = 0.78-4.08), delivery route (OR = 2.8, 95% CI = 1.36-5.76) and birth rank (OR = 1.8, 95% CI = 0.96-3.38).

Final model includes following variables with significant statistical association ( $p$  value < 0.05): close consanguinity (adjusted odds ratio (AOR) = 5.23), prematurity (AOR = 5.57), LBW (AOR = 7.68), C-section (AOR = 7.27), birth rank more than 3 (AOR = 6.95) and births spacing less than 24 months (AOR = 4.65) (Table 2).

## Discussion

This study shows that first cousin marriages, prematurity, LBW, C-section, birth spacing less than 24 months and birth rank more than 3 were potential risk factors for neonatal death.

In this study, an increased risk of neonatal death was found in the consanguineous group and this finding is consistent with previous similar studies in Iran (9,15). Also the observed association is in the same direction as that demonstrated by researchers on evaluation of consanguineous marriages and children mortality correlation (5-8,12,16).

In this study, gender of neonate was not a risk factor which is consistent with results of a study done in Kurdistan Province of Iran. But delivery route

**Table 1:** Distribution of risk factors among cases and controls and ORs from univariate conditional logistic regression; a Nested Case-Control study in a rural part of Iran

Variables	Cases n (%)	Controls n (%)	OR (95% CI)
Sex of neonate			
Female	43 (44.3%)	52 (53.6%)	1
Male	54 (55.7%)	45 (46.4%)	1.43 (0.82-2.50)
Birth weight			
≥2500gr	46 (47.4%)	91 (91.8%)	1
<2500gr	51 (52.6%)	6 (8.2%)	9.8 (3.90-24.60)
Gestational age			
≥37 weeks	50(51.5%)	89(91.8%)	1
<37 weeks	47(48.5%)	8(8.2%)	8.8 (3.50-22.20)
Delivery type			
NVD	66 (68%)	84 (86.6%)	1
C-section	31(32%)	13 (13.4%)	2.8 (1.36-5.76)
Birth rank:			
< 3	63 (64.9%)	75 (77.3%)	1
≥ 3	34 (35.1%)	22 (22.7%)	1.8 (0.96-3.38)
Birth spacing			
≥24 months	46 (47.4%)	56 (57.7%)	1
<24 months	19 (19.6%)	13 (13.4%)	1.79 (0.78-4.08)
First gestation	32 (33%)	28 (28.9%)	-
Maternal age			
≥18 or ≤ 35	84 (86.6%)	88 (90.7%)	1
< 18 or > 35	13 (13.4%)	9 (9.3%)	1.5 (0.61-3.67)
Parents Relative			
Non-familial	54 (55.7)	60 (61.9)	1
Distant relatives	34 (35.1)	24 (24.7)	0.74 (0.30- 1.85)
First Cousins	9 (9.3)	13 (13.4)	1.5 (0.84- 2.95)

**Table 2:** Results of Multivariate conditional logistic regression of neonatal mortality risk factors; a Nested Case-Control study in a rural part of Iran

Variables	Adjusted OR	95% CI	p value
Birth weight			
≥2500gr	1	-	-
<2500gr	7.68	1.49- 39.55	0.015
Gestational age			
≥37 weeks	1	-	-
<37 weeks	5.57	1.12- 27.60	0.035
Consanguinity			
Unrelative	1	-	-
Second Cousin	0.31	0.07- 1.4	0.126
First Cousin	5.23	1.59- 17.21	0.007
Birth rank			
≤3	1	-	-
>3	6.95	1.90- 25.28	0.003
Delivery route			
NVD	1	-	-
C-section	7.27	2.05- 25.72	0.002
Birth Spacing			
≥24 months	1	-	-
<24 months	4.65	1.13-19.13	0.033

(C-section) which did not have a significant effect in the above-mentioned study, revealed higher OR with significant statistical association in present study (17).

Our observations are similar to a case-control study which was conducted in Brazil and the results indicated that prematurity and LBW were risk factors for neonatal death. They did not estimate significant OR for delivery route but we identified C-section as an important risk factor. Neither of the studies showed significant correlation between maternal age and neonatal death (18). In this research, the effects of prematurity and LBW on neonatal mortality were similar to the findings of a research performed by a group of investigators in the city of Yazd in Iran, but contrary to our results regarding the effect of gender, they reported the determinant effect of gender. Present study shows that birth spacing less than 24 months increases the risk of neonatal death but in that study birth intervals less than 12 months was identified as a potential risk factor (19). There were significant positive associations between neonatal death and prematurity, LBW, maternal age older than 35 years and birth rank higher than 5 in Shirvani and colleagues' survey (20).

Numerous investigations have shown that LBW with or without prematurity plays in a complex causal framework of neonatal death, involving genetic and environmental factors related to socioeconomic status (21- 23). Thus, as a limitation of this research, it is focused on main risk factors of neonatal death and our suggestion is extension of nested case-control study to all probable maternal, neonatal and socioeconomic risk factors of neonatal mortality.

## Conclusion

The key findings of the present study is a significant positive association between close consanguinity and neonatal death, after controlling the effects of prematurity, LBW, C-section, birth spacing less than 24 months and birth rank more than 3.

## Acknowledgments

Authors wish to thank Yasuj Medical University staff especially Mrs F. Sadeghi, Mr Z. Parisay, Mr K. Davari and Mr S. Rezaei, for their efforts in data collection.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Funding

This research was supported by Tehran University of Medical Sciences, Iran.

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