Association of caesarean section and neonatal death: a population-based case–control study in Islamic Republic of Iran

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الارتباط بين العملية القيصرية ووفيات حديثي الولادة: دراسة حالات وشواهد قائمة على السكان في جمهورية إيران الإسلامية

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الخلاصة: إن ارتفاع معدّل العمليات القيصرية في جمهورية إيران الإسلامية يمكن أن يكون عامل خطر بالنسبة للنتائج الضارة لحديثي الولادة. وقد قامت دراسة الحالات والشواهد القائمة على السكان هذه باستقصاء الارتباط بين العملية القيصرية ووفيات حديثي الولادة. فتمت مقارنة ما مجموعه 146 أماً توفي أطفالهن خلال الـ 28 يوماً التالية للولادة مع 549 أماً لديهن مواليد أحياء، من حيث طريق الولادة وأسباب خضوعهن للعملية القيصرية. فكانت نسبة الأرجحية لارتباط العملية القيصرية بوفيات حديثي الولادة 1.97 (1.35-2.87). وكانت نسبة الأرجحية المعدَّلة 2.19 (1.48–3.24) عند الأخذ في الاعتبار والتعديل حسب مستوى تعليم الأم وسنها وترتيب الولادة. ونسبة الأرجحية المعدلة بالنسبة للقيصرية الاختيارية والقيصرية السابقة والقيصرية الاضطرارية كانت 0.65 (0.26–1.62) و 2.77 (1.64–4.66) و 2.51 (1.56-4.03) على التوالي. لقد اختلفت نسب الأرجحية بالنسبة للعملية القيصرية ووفيات حديثي الولادة بحسب مستوى تعليم الأم وسنها وترتيب الولادة. إن الارتباط بين العملية القيصرية ووفيات حديثي الولادة أمر معقّد، ويتغيَّر بفعل عوامل مؤثرة أخرى.

ABSTRACT The high caesarean section rate in the Islamic Republic of Iran could be a risk for adverse neonatal outcomes. This population-based, case–control study investigated the association of caesarean section and neonatal death. A total of 146 mothers whose babies had died during 28 days after birth were compared with 549 mothers with live newborns, according to delivery route and reasons for undergoing caesarean section. The crude odds ratio (OR) for the association of caesarean section and neonatal death was 1.97 (1.35–2.87). The adjusted OR was 2.19 (1.48–3.24) controlled for mother's education, parity and age. Adjusted ORs for elective caesarean, previous caesarean and emergency caesarean were 0.65 (0.26–1.62), 2.77 (1.64–4.66) and 2.51 (1.56–4.03) respectively. The ORs for caesarean delivery and neonatal death varied by mother's education, parity and age. The association of caesarean section with neonatal death is complex and is modified by other influencing factors.

Association entre césarienne et décès néonatal : étude cas-témoin populationnelle en République islamique d'Iran

RÉSUMÉ Le taux élevé de césariennes en République islamique d'Iran pourrait représenter un risque d'issues néonatales défavorables. La présente étude cas-témoin populationnelle a évalué l'association entre la césarienne et le décès néonatal. Au total, 146 mères dont l'enfant était décédé dans les 28 jours suivant la naissance ont été comparées à 549 mères dont le nouveau-né était vivant, en tenant compte de la voie d'accouchement et des motifs ayant mené à pratiquer une césarienne. L'*odds ratio* brut pour l'association entre la césarienne et le décès néonatal était de 1,97 (1,35–2,87). L'*odds ratio* corrigé pour l'âge, le niveau d'études et la parité de la mère était de 2,19 (1,48–3,24). L'*odds ratio* corrigé pour une césarienne programmée, une première césarienne et une césarienne d'urgence était de 0,65 (0,26–1,62), 2,77 (1,64–4,66) et 2,51 (1,56–4,03) respectivement. L'*odds ratio* pour un accouchement par césarienne et le décès néonatal variait en fonction du niveau d'études de la mère, de la parité et de son âge. L'association entre la césarienne et le décès néonatal est complexe et elle est modifiée par d'autres facteurs d'influence.

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Received: 09/07/14; accepted: 23/02/15

Introduction

Perinatal mortality is a leading cause of years of life lost worldwide (*1*). A neonatal death is defined as death occurring during the first 28 days of life. The neonatal mortality rate, which is defined as the number of neonatal deaths per 1000 live births, is an important health indicator (*2*). Various factors including socioeconomic status, cultural factors and the mother's condition during pregnancy contribute to neonatal death.

Many studies have reported that delivery using caesarean section is a risk factor for adverse maternal and neonatal outcomes. Nonetheless, the caesarean section rate has been increasing over recent decades (*3,4*) in both developed and developing countries (*5–7*). Because of the evidence of the increase in both maternal and neonatal negative outcomes of caesarean section the Joint Interregional Conference on Appropriate Technology for Birth in 1985 advised a caesarean section rate lower than 10–15% for all regions of world (*8*).

Ecological studies have reported differing and sometimes controversial results about the association between the rate of caesarean section and the rate of neonatal mortality. In a study in Latin America, an increase in the caesarean section rate in the range 10–20% accompanied an increase in the neonatal mortality rate (*9*). Another study carried out in 193 countries from 2000–09 showed that in countries where the caesarean section rate was lower than 15% caesarean section delivery was negatively associated with neonatal mortality rate, while in the countries with caesarean section rates higher than 15% the association was positive (*10*). In addition, the caesarean section rate and neonatal mortality rate were not associated in high- and middle-income countries, while there was a negative association between the two rates in lower income countries, as reported by a study carried out in 119 countries from 1991 to 2003. Althabe et al. concluded that availability of caesarean section in low-income countries could improve pregnancy outcomes including neonatal mortality rate (*11*).

There are also reports on the association between caesarean section and neonatal death in observational studies based on individual data. In a case–control study in the Islamic Republic of Iran, the risk of neonatal death in caesarean section deliveries was 3.34 times that of normal vaginal deliveries (*12*). However, the association reported between caesarean section and neonatal death differed depending on the indication for caesarean section. The findings of a study in Africa showed that although emergency caesarean section was associated with a higher risk of neonatal death, elective caesarean section lowered the risk of neonatal death (*13*). Another study in the United States showed that planned caesarean section increased the risk of neonatal death compared with planned vaginal delivery (*14*). Some factors, such as socioeconomic status, indications for caesarean section and neonatal and maternal anthropometry, may confound the association with caesarean section.

The Islamic Republic of Iran has been reported to have the second highest caesarean section rate in the world after Brazil (*15*). This rate has been rising in recent years (*5,16*). However, available evidences on the relationship between caesarean section and neonatal death come from ecological studies that are usually unable to provide strong evidence, or from secondary case–control studies which often suffer from selection bias and confounding. There have therefore been few population-based studies with clear objectives and valid methodologies, even in other developing countries. To the best of our knowledge, this is the first population-based, case–control study in the Islamic Republic of Iran aiming at investigating the association between caesarean section and neonatal death and related factors.

Methods

The present study is part of a population-based, case–control study to investigate related factors in neonatal death and stillbirth in Bushehr, a southern province of the Islamic Republic of Iran.

Sample

All mothers in 9 districts of Bushehr province whose neonate died within the 1-year period 23 September 2011 to 22 September 2012 were included as cases. A total number of 18 321 births were registered in the same period in the province. Neonatal death was defined as death due to any reason during the first 28 days of life. For each case (neonatal death or stillbirth), 2 controls were randomly selected from among mothers who had had a delivery around the time that a case of neonatal death or stillbirth occurred in the same district but whose neonate was alive 28 days after birth. Controls were selected such that the case and control groups were comparable in terms of mean age and residential status (urban/rural). As stillbirth itself might be an indication for caesarean section, we excluded stillbirth cases in this study, but for the purpose of increasing statistical power, all controls (both for neonatal deaths and stillbirths) remained in the analyses.

Interviewers visited mothers at home and invited them to participate. The response rate was 100% and all mothers with neonatal deaths and control mothers invited to participate in the study accepted the invitation. There were also no drop-outs at the end of neonatal period.

This study was approved by the research committee of Bushehr University of Medical Sciences. Permission was also obtained from the Deputy for Health of the University to access

household files in rural and urban heath centres. The objectives of the study were explained to all the participants, and verbal consent was obtained for inclusion in the study.

Data collection

The population coverage of health services is 100% in Bushehr province. It means that every household has a file in the public health centre where the household members are registered and the records of delivery type are complete. Moreover, about 99.6% of babies were born in hospitals.

Data were recorded in a form developed by the investigator. The questions were designed to include demographic variables, as well as data on the delivery route (caesarean section or vaginal delivery) and history of delivery (including order of this pregnancy). Data on demographic variables was obtained through the direct face-to-face questioning of the mothers by 9 trained interviewers (an interviewer for each district) and data on the route and history of delivery by reviewing household files in health centres.

All interviewers were selected among expert staff of the health system and trained before data collection in a training meeting. A supervisor at the provincial level was available for interviewers for further questions during data collection. The face validity of the questionnaire was checked through asking a number of experts to read and approve the validity of questions. To minimize the number of recall errors, the questionnaires were completed a short time after the occurrence of neonatal death in the cases or after the first month of birth in the controls. All the data collected by interviewers were checked for possible errors by the supervisor before data entry.

Vaginal delivery was defined as a delivery after the 22nd week of gestation through the birth canal caused by uterine contractions, with or without instruments and with or without episiotomy by a midwife, obstetrics specialist physician, or without their assistance at home, in hospital, or any other place. Caesarean section was defined as a delivery in which the neonate was taken out through laparotomy (incision on the abdomen) or hysterectomy (incision on the uterus) by an obstetric specialist physician. Emergency caesarean section was defined as an unplanned caesarean section performed because of any maternal or fetal indication. A caesarean section was elective if it was a pre-planned operation without any specific indication and based on the contingency decision by the parents and the obstetrician. The operation was called repeat caesarean section if there was no other indications other than a previous caesarean section.

Statistical analysis

The data collected from the case and control groups was described using mean and standard deviation (SD) for continuous variables and absolute and relative frequencies for categorical variables. A chi-squared test was used to compare the frequencies between the 2 groups. Odds ratio (OR) and 95% confidence interval (CI) were used to show the association between dichotomous variables and neonatal death. Multiple logistic regression models were used to control for potential confounding variables. Clinically and logically meaningful independent variables were initially selected. Directed acyclic graph criteria were used for the selection of the variables to include in this stage (*17*). Then variables with a significance level < 0.2 in the univariate test between dependent and independent variables were included in the multiple logistic regression models. Finally, Hosmer–Lemshow goodness-of-fit test was used to select the best models. As the result, mother's age at pregnancy, mother's education and parity were included, and residence, mother's employment and neonate's sex were excluded from the model. In the first model, the dichotomous variable of neonatal death was included as a dependent variable. The independent variables were delivery type (caesarean section, vaginal delivery), education level (illiterate: none, low: primary or secondary school, high: high school and more), parity (1, 2, 3, ≥ 4), and mother's age (< 18, 18–35, > 35 years). The second model was the same as the first one, except for the independent variable of study type, which was included as an indicator variable of 4 groups (vaginal delivery, emergency caesarean section, elective caesarean section, repeat caesarean section). The significance level was 0.05 for all statistical tests. Data analyses were performed by using *Stata* software, version 11.

Results

Demographic and socioeconomic characteristics

A total of 146 mothers with neonates who died and 549 mothers with neonates still alive were included in the study. The mean age of all the participants was 27.5 (SD 5.7) years [27.6 (SD 6.2) and 27.5 (SD 5.6) years for the case and control groups respectively]. The proportion of high-risk pregnancies (mother's age < 18 or > 35 years) were 11% and 9.1% for the case and control groups respectively. About 50% and 75% of neonates were dead within 3 and 7 days of birth respectively. The mean age of neonatal death was 5.5 days. Table 1 shows the demographic and socioeconomic characteristics of the participants in the case and control groups.

Frequencies of delivery types

Comparison of the frequencies of delivery type between the cases and controls showed that 94 (64.4%) of deliveries in the cases and 263 (47.9%) of deliveries in the controls were caesarean section, which was a statistically significant difference ($\chi^2 = 12.5$; $P < 0.001$).

Table 1 Demographic and socioeconomic characteristics of mothers with neonatal deaths (cases) and mothers with live neonates (controls)

Variable	Cases (n = 146)		Controls (n = 549)		P-value
Mother's age [mean (SD)]	27.6 (6.2)		27.5 (5.6)		0.850
Mother's education level [no. (%)]					
None	20	13.7	44	8.0	0.004
Low	60	41.1	176	32.1	
High	66	45.2	329	59.9	
Residence [no. (%)]					
Urban	82	59.0	391	74.1	0.001
Rural	57	41.0	137	25.9	
Mother's employment [no. (%)]					
Employed (at home)	4	2.7	14	2.6	0.731
Employed (outside)	11	7.5	53	9.7	
Housekeeper	131	89.7	482	87.8	
Neonate's sex [no. (%)]					
Male	82	56.6	288	52.5	0.426
Female	63	43.4	248	45.2	
Both (twins)	0		13	2.3	
Parity [no. (%)]					
1	42	28.8	210	38.3	0.008
2	51	34.9	194	35.3	
3	22	15.1	84	15.3	
≥ 4	31	21.2	61	11.1	
Caesarean section delivery [no. (%)]	94	64.4	263	47.9	< 0.001
Caesarean section type [no. (%)]					
Elective	6	6.5	60	23.2	0.002
Repeat	40	43.5	86	33.2	
Emergency	46	50.0	113	43.6	

Variables associated with neonatal death

Crude OR for the association of caesarean section and neonatal death was 1.97 (95% CI: 1.35–2.87). Adjusted OR after controlling for the confounding effects of mother's age, number of pregnancies and educational level was 2.19 (95% CI: 1.48–3.24), as shown in model 1 on Table 2. In model 2, analysed by indication for caesarean section, the adjusted ORs for the association of neonatal death and elective caesarean section, repeat caesarean section and emergency caesarean section were 0.65 (95% CI: 0.26–1.62), 2.77 (95% CI: 1.64–4.66) and 2.51 (95% CI: 1.56–4.03) respectively (Table 2).

Univariate analysis showed a statistically significant negative association between mother's educational level and neonatal death (χ^2 = 11.2; P = 0.004). This association was also seen after controlling for potential confounders (Table 2). In addition, the association between caesarean section and neonatal death was different according to mother's level of education (Table 3).

Neonatal death was also associated with parity (χ^2 = 11.8; P = 0.008). This association remained statistically significant after adjusting for potential confounders (Table 2). In addition, association between delivery type and neonatal death differed according to parity. This association was not statistically significant in the first and third pregnancies, but it was significant in the second and fourth pregnancies. OR was estimated at 4.33 (95% CI: 1.56–12.5) for parities of 4 and more (Table 3).

The association between caesarean section and neonatal death also differed according to mother's age (Table 3). For mothers aged 18–35 years OR was 1.87, while for mothers younger than 18 years old or older than 35 years (higher risk age group), OR was 3.0 (the association, however, was not statistically significant).

Indications for caesarean section

Analysing all mothers (cases and controls) with caesarean section delivery, we found that 69.0% of first pregnancies

Table 2 Results of multivariable logistic regression models for risk factors for neonatal death

Variable	Risk of neonatal death	
	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
Delivery type		
Vaginal (Ref.)	1.00	1.00
Caesarean section	2.19 (1.48–3.24)	–
Elective caesarean section	–	0.65 (0.26–1.62)
Repeat caesarean section	–	2.77 (1.64–4.66)
Emergency caesarean section	–	2.51 (1.56–4.03)
Mother's education		
High (Ref.)	1.00	1.00
Low	2.12 (1.08–4.18)	1.91 (0.94–3.85)
None	1.67 (1.10–2.53)	1.61 (1.05–2.45)
Parity		
1 (Ref.)	1.00	1.00
2	1.36 (0.85–2.16)	1.14 (0.68–1.89)
3	1.18 (0.65–2.17)	0.95 (0.48–1.89)
≥ 4	2.55 (1.35–4.80)	2.51 (1.28–4.93)
Mother's age (years)		
18–35 (Ref.)	1.00	1.00
< 18	1.51 (0.35–6.51)	1.33 (0.31–5.75)
> 35	0.56 (0.29–1.07)	0.49 (0.25–0.98)

OR = odds ratio; CI = confidence interval; (Ref.) = reference group; – = not applicable.

were emergency caesarean sections, while for second and more pregnancies a history of previous caesarean section was the most frequent indication for caesarean section. For mothers in the higher-risk age groups (< 18 and > 35 years) 52.8% of caesarean sections were emergency caesarean section, while for those aged 18–35 years 44.4% were emergency caesarean section. In contrast, elective caesarean section rates were 11.1% and 19.7% for mothers in the higher and lower risk age groups respectively. There was no statistically significant association between delivery type and mother's educational level (χ^2 = 3.0; P = 0.225; statistical power = 67%).

Table 3 Crude odds ratios (OR) and 95% confidence interval (CI) for the association between caesarean section and neonatal death at different levels of potential confounders

Variable	OR (95% CI)
Overall (adjusted)	2.19 (1.48–3.24)
Education	
None	1.94 (0.58–6.50)
Low	2.38 (1.25–4.63)
High	1.89 (1.05–3.47)
Parity	
1	1.36 (0.66–2.82)
2	2.71 (1.34–2.77)
3	0.99 (0.35–2.77)
≥ 4	4.55 (1.56–12.50)
Mother's age (years)	
< 18 / > 35	3.00 (0.76–14.30)
18–35	1.87 (1.24–2.85)

Discussion

The findings of the present study showed that caesarean section was associated with an increased risk of neonatal death. This association remained statistically significant after adjusting for potential confounders. Elective caesarean section was not associated with neonatal death. However, emergency caesarean section and repeat caesarean section due to previous caesarean section were positively associated with neonatal death. The association between caesarean section and neonatal death differed according to the mother's education level, order of pregnancy and age.

The results showed that caesarean section was associated with neonatal death. In the United States, MacDorman et al. found that the rate of neonatal death in caesarean section births was 2.9 times the rate in vaginal delivery births in full-term neonates whose mothers did not have medical risks or labour complications (*18*). This finding might be explained by the release of fetal catecholamines and prostaglandins, which causes surfactant synthesis, compression of the infant's chest in the birth canal, respiratory diseases and release of adrenaline during labour in vaginal delivery (*18–20*). However, some studies did not confirm a positive association between caesarean section and neonatal death (*21,22*). Some even reported that the risk of neonatal death was lower in caesarean section deliveries (*13,23*). It seems that

this association is complex. The type and indication for caesarean section, the expertise and knowledge of the obstetrician and the quality of care in health facilities are all factors that could modify the association.

Another finding of the present study was that emergency caesarean section was associated with an increased risk of neonatal death compared with vaginal delivery. Some studies reported the same results (*13*). The presence of maternal or fetal underlying conditions such as abnormal presentation, prolonged labour, fetal distress or delay in providing care can explain such a finding. Additional factors included caesarean section being carried out by less experienced teams who often work at peripheral levels in emergency rooms. However, it is not clear whether emergency caesarean section is the cause of neonatal death or the indication for which caesarean section is performed.

Compared with vaginal delivery, elective caesarean section was not associated with neonatal death. However, in cases of repeat caesarean section (due to history of previous caesarean section), risk of neonatal death was higher than the risk in vaginal delivery. As in elective caesarean section, repeat caesarean sections are done with a previous consent and plan, so this finding cannot be related to unpredicted conditions such as those in the case of emergency caesarean section. Although some studies reported that the risk of neonatal death in planned caesarean section was lower than the risk in vaginal delivery (*13*), others showed that caesarean section increased the risk of neonatal death in subsequent deliveries (*24*). This result might be partly because the indications for the first caesarean section are the same at the next delivery (*25*).

Caesarean section doubled the risk of neonatal death in mothers with no education. Models 1 and 2 in the regression analysis showed that mother's educational level had a statistically significant association with neonatal death. In addition, the majority of caesarean sections in mothers with no education were emergency and repeat caesarean sections, in which the risk of neonatal death was higher. Therefore, a positive association between caesarean section and neonatal death in mothers with no education is logical. However, this association was not statistically significant, probably because of inadequate statistical power as the result of the small number of mothers with no education.

This complexity was shown in the association between caesarean section and neonatal death by parity. The associations were significant in the second and fourth orders of pregnancy but not in the first and third orders. MacDorman et al. reported that the caesarean section/vaginal delivery ratio of neonatal mortality rates in multiparous women was higher than in primiparous women (*18*). The statistically significant association is justifiable for women of parity ≥ 4, as these women are older and more likely to come from lower socioeconomic groups (*18*). However, we could not find any explanation for the results of other parities. Therefore, we can only conclude that the effect of parity on the association is not linear.

The association between caesarean section and neonatal death also differed according to mother's age. In the lower-risk age group, i.e. 18–35 years, this association was the same as the overall association. However, in higher-risk age groups, i.e. < 18 years and > 35 years, there was a stronger association, which could be because of the higher frequency of emergency caesarean sections in these age groups. MacDorman et al. reported a higher caesarean section/vaginal delivery ratio of neonatal mortality rates in mothers older than 35 years that is consistent with this finding. However, because of the small number of participants in these age groups, the statistical power might have been inadequate.

This study had both strengths and limitations. This research was a well-designed population-based, case–control study conducted in Islamic Republic of Iran, a developing country in which the rate of caesarean section is relatively high. The limited sample size is an important limitation of the present study. Although the study included all neonatal deaths that occurred in one province during one year, which provided a relatively good sample size, the statistical power was not adequate for subgroup analyses. In addition, because more reliable information on some potential confounders was not available, controlling for these factors was not complete and there was a risk of residual confounding.

Conclusion

This study showed that although caesarean section can be considered a risk factor for neonatal death, the association between caesarean section and neonatal death had complexities and was modified by the effects of other factors. Moreover, because of possible biases and strong confounders in retrospective case–control studies, further large, prospective cohort studies are needed to investigate the unknown aspects of the relationship between caesarean section and neonatal death, especially in the developing world.

Acknowledgements

The authors would like to thank the staff of the district health centres of Bushehr province for their sincere assistance in the data gathering.

Funding: This study was carried out by financial support of the Deputy for Health of Bushehr University of Medical Sciences.

Competing interests: None declared.

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